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(71) Applicant *(for all designated States except US)*: **TARGACEPT, INC.** [US/US]; Post Office Box 1487, Winston-Salem, NC 27102-1487 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SCHMITT, Jeffrey, Daniel** [US/US]; 632 Laurel Street, Winston-Salem, NC (US). **DULL, Gary, Maurice** [US/US]; 6025 Shallowford Road, Lewisville, NC (US). **BHATTI, Balwinder, Singh** [US/US]; 2536 Polo Road, Winston-Salem, NC (US).

(74) Agent: **SAJOVEC, F., Michael**; Myers, Bigel, Sibley, & Sajovec, P.A., P.O. Box 37428, Raleigh, NC 27627 (US).

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(54) Title: ARYL OLEFINIC AZACYCLIC, AND ARYL ACETYLENIC AZACYCLIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS INHIBITORS OF NICOTINIC CHOLINERGIC RECEPTORS

(57) Abstract: Patients susceptible to or suffering from conditions and disorders, such as central nervous system disorders, are treated by administering to a patient in need thereof aryl olefinic azacyclic compounds and aryl acetylenic azacylic compounds, including pyridyl olefinic cycloalkylamines and pyridyl acetylenic cycloalkylamines. Exemplary compounds include (S)-(E)-3-(3-pyrrolidin-2-yl-prop-1-enyl)pyridine, (S)-(E)-3-(2-pyrrolidin-2-ylvinyl)pyridine, 3-(2-pyrrolidin-2-ylethenyl)pyridine, 3-(3-pyrrolidin-2-ylprop-1-enyl)pyridine, 3-(2-(2-azetidinyl)ethenyl)pyridine, 3-(3-(2-azetidinyl) prop-1-enyl)pyridine, 2-(2-(3-pyridyl)ethenyl)-1-azabicyclo[3.3.0]octane, 2-(3-(3-pyridyl)prop-2-enyl)-1-azabicyclo[3.3.0]octane, 3-(2-(3-pyridyl)ethenyl)-2-azabicyclo[2.2.1]heptane, 3-(3-(3-pyridyl)prop-2-enyl)-2-azabicyclo[2.2.1]heptane, 2-(2-(3-pyridyl)ethenyl)-7-azabicyclo[2.2.1]heptane, 2-(3-(3-pyridyl)prop-2-enyl)-7-azabicyclo[2.2.1]heptane, 2-(2-(3-pyridyl)ethenyl)quinuclidine and 2-(3-(3-pyridyl)prop-2-enyl)quinuclidine.

ARYL OLEFINIC AZACYCLIC, AND ARYL ACETYLENIC AZACYCLIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS INHIBITORS OF NICOTINIC CHOLINERGIC RECEPTORS

Background of the Invention

The present invention relates to pharmaceutical compositions, and particularly pharmaceutical compositions incorporating compounds that are capable of affecting nicotinic cholinergic receptors. More particularly, the present invention relates to compounds capable of activating nicotinic cholinergic receptors, for example, as agonists of specific nicotinic receptor subtypes. The present invention also relates to methods for treating a wide variety of conditions and disorders, and particularly conditions and disorders associated with dysfunction of the central and autonomic nervous systems.

Nicotine has been proposed to have a number of pharmacological effects. See, for example, Pullan et al. *N. Engl. J. Med.* 330:811-815 (1994). Certain of those effects may be related to effects upon neurotransmitter release. See for example, Sjak-shie et al., *Brain Res.* 624:295 (1993), where neuroprotective effects of nicotine are proposed. Release of acetylcholine and dopamine by neurons upon administration of nicotine has been reported by Rowell et al., *J. Neurochem.* 43:1593 (1984); Rapier et al., *J. Neurochem.* 50:1123 (1988); Sandor et al., *Brain Res.* 567:313 (1991) and Vizi, *Br. J. Pharmacol.* 47:765 (1973). Release of norepinephrine by neurons upon administration of nicotine has been reported by Hall et al., *Biochem. Pharmacol.* 21:1829 (1972). Release of serotonin by neurons upon administration of nicotine has been reported by Hery et al., *Arch. Int. Pharmacodyn. Ther.* 296:91 (1977). Release of glutamate by neurons upon administration of nicotine has been reported by Toth et al., *Neurochem Res.* 17:265 (1992). In addition, nicotine reportedly potentiates the

pharmacological behavior of certain pharmaceutical compositions used for the treatment of certain disorders. See, Sanberg et al., *Pharmacol. Biochem. & Behavior* 46:303 (1993); Harsing et al., *J. Neurochem.* 59:48 (1993) and Hughes, *Proceedings from Intl. Symp. Nic.* S40 (1994). Furthermore, various other beneficial pharmacological effects of nicotine have been proposed. *See*, Decina et al., *Biol. Psychiatry* 28:502 (1990); Wagner et al., *Pharmacopsychiatry* 21:301 (1988); Pomerleau et al., *Addictive Behaviors* 9:265 (1984); Onaivi et al., *Life Sci.* 54(3):193 (1994); Tripathi et al., *JPET* 221: 91-96 (1982) and Hamon, *Trends in Pharmacol. Res.* 15:36.

Various nicotinic compounds have been reported as being useful for treating a wide variety of conditions and disorders. See, for example, Williams et al. *DN&P* 7(4):205-227 (1994), Arneric et al., *CNS Drug Rev.* 1(1):1-26 (1995), Arneric et al., *Exp. Opin. Invest. Drugs* 5(1):79-100 (1996), Bencherif et al., *JPET* 279:1413 (1996), Lippiello et al., *JPET* 279:1422 (1996), Damaj et al., *Neuroscience* (1997), Holladay et al., *J. Med. Chem* 40(28): 4169-4194 (1997), Bannon et al., *Science* 279: 77-80 (1998), PCT WO 94/08992, PCT WO 96/31475, PCT WO 96/40682, and U.S. Patent Nos. 5,583,140 to Bencherif et al., 5,597,919 to Dull et al., 5,604,231 to Smith et al., 5,852,041 to Cosford et al. and 5,952,239 to Becherif et al. Nicotinic compounds are reported as being particularly useful for treating a wide variety of Central Nervous System (CNS) disorders.

CNS disorders are a type of neurological disorder. CNS disorders can be drug induced; can be attributed to genetic predisposition, infection or trauma; or can be of unknown etiology. CNS disorders comprise neuropsychiatric disorders, neurological diseases and mental illnesses; and include neurodegenerative diseases, behavioral disorders, cognitive disorders and cognitive affective disorders. There are several CNS disorders whose clinical manifestations have been attributed to CNS dysfunction (i.e., disorders resulting from inappropriate levels of neurotransmitter release, inappropriate properties of neurotransmitter receptors, and/or inappropriate interaction between neurotransmitters and neurotransmitter receptors). Several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency and/or a serotonergic deficiency. CNS disorders of relatively common occurrence include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), Parkinsonism including Parkinson's

disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, dyslexia, hypoxia, schizophrenia and Tourette's syndrome.

It would be desirable to provide a useful method for the prevention and treatment of a condition or disorder by administering a nicotinic compound to a patient susceptible to or suffering from such a condition or disorder. It would be highly beneficial to provide individuals suffering from certain disorders (e.g., CNS diseases) with interruption of the symptoms of those disorders by the administration of a pharmaceutical composition containing an active ingredient having nicotinic pharmacology and which has a beneficial effect (e.g., upon the functioning of the CNS), but which does not provide any significant associated side effects. It would be highly desirable to provide a pharmaceutical composition incorporating a compound which interacts with nicotinic receptors, such as those which have the potential to effect the functioning of the CNS, but which compound when employed in an amount sufficient to effect the functioning of the CNS, does not significantly effect those receptor subtypes which have the potential to induce undesirable side effects (e.g., appreciable activity at skeletal muscle sites).

Summary of the Invention

The present invention relates to aryl olefinic azacyclic compounds and aryl acetylenic azacylic compounds, including pyridyl olefinic cycloalkylamines and pyridyl acetylenic cycloalkylamines. The present invention also relates to prodrug derivatives of the compounds of the present invention. Exemplary compounds of the present invention are (S)-(E)-3-(3-pyrrolidin-2-yl-prop-1-enyl)pyridine, (S)-(E)-3-(2-pyrrolidin-2-ylvinyl)pyridine, 3-(2-pyrrolidin-2-ylethenyl)pyridine, 3-(3-pyrrolidin-2-ylprop-1-enyl)pyridine, 3-(2-(2-azetidinyl)ethenyl)pyridine, 3-(3-(2-azetidinyl)prop-1-enyl)pyridine, 2-(2-(3-pyridyl)ethenyl)-1-azabicyclo[3.3.0]octane, 2-(3-(3-pyridyl)prop-2-enyl)-1-azabicyclo[3.3.0]octane, 3-(2-(3-pyridyl)ethenyl)-2-azabicyclo[2.2.1]heptane, 3-(3-(3-pyridyl)prop-2-enyl)-2-azabicyclo[2.2.1]heptane, 2-(2-(3-pyridyl)ethenyl)-7-azabicyclo[2.2.1]heptane, 2-(3-(3-pyridyl)prop-2-enyl)-7-azabicyclo[2.2.1]heptane, 2-(2-(3-pyridyl)ethenyl)quinuclidine and 2-(3-(3-pyridyl)prop-2-enyl)quinuclidine. The compounds of the present invention function as agonists, and bind specifically to certain nicotinic receptors.

The present invention also relates to methods for the prevention or treatment of a wide variety of conditions or disorders, and particularly those disorders characterized by disfunction of nicotinic cholinergic neurotransmission including disorders involving neuromodulation of neurotransmitter release, such as dopamine release. The present invention also relates to methods for the prevention or treatment of disorders, such as central nervous system (CNS) disorders, which are characterized by an alteration in normal neurotransmitter release. The present invention also relates to methods for the treatment of certain conditions (e.g., a method for alleviating pain). The methods involve administering to a subject an effective amount of a compound of the present invention. As such, the present invention relates to a method for using the compounds of the present invention for the manufacture of pharmaceutical compositions for the treatment of a wide variety of diseases and disorders.

The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of a compound of the present invention. Such a pharmaceutical composition incorporates a compound which, when employed in effective amounts, has the capability of interacting with relevant nicotinic receptor sites of a subject, and hence has the capability of acting as a therapeutic agent in the prevention or treatment of a wide variety of conditions and disorders, particularly those disorders characterized by an alteration in normal neurotransmitter release. Preferred pharmaceutical compositions comprise compounds of the present invention.

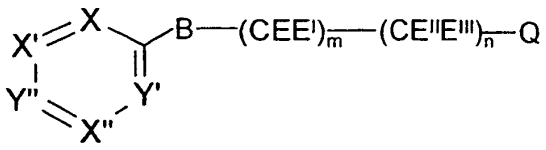
The pharmaceutical compositions of the present invention are useful for the prevention and treatment of disorders, such as CNS disorders, which are characterized by an alteration in normal neurotransmitter release. The pharmaceutical compositions provide therapeutic benefit to individuals suffering from such disorders and exhibiting clinical manifestations of such disorders in that the compounds within those compositions, when employed in effective amounts, have the potential to (i) exhibit nicotinic pharmacology and affect relevant nicotinic receptors sites (e.g., act as a pharmacological agonist to activate nicotinic receptors), and (ii) elicit neurotransmitter secretion, and hence prevent and suppress the symptoms associated with those diseases. In addition, the compounds are expected to have the potential to (i) increase the number of nicotinic cholinergic receptors of the brain of the patient, (ii) exhibit neuroprotective effects and (iii) when employed in effective amounts do not cause appreciable adverse side effects (e.g., significant increases in blood pressure and heart rate, significant negative effects upon the gastro-intestinal tract, and

significant effects upon skeletal muscle). The pharmaceutical compositions of the present invention are believed to be safe and effective with regards to prevention and treatment of a wide variety of conditions and disorders.

The foregoing and other aspects of the present invention are explained in detail in the detailed description and examples set forth below.

Detailed Description of the Invention

The compounds of the present invention include compounds of the formula:



where Q is defined hereinafter; and each of X, X', X", Y' and Y" are individually nitrogen, nitrogen bonded to oxygen (e.g., an N-oxide or N-O functionality) or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, and generally greater than 0.2, and even greater than 0.3; less than 0 and generally less than -0.1; or 0; as determined in accordance with Hansch et al., *Chem. Rev.* 91:165 (1991). When any of X, X', X", Y' and Y" are carbon bonded to a substituent species, those substituent species typically have a sigma m value between about –0.3 and about 0.75, frequently between about -0.25 and about 0.6; and each sigma m value individually can be 0 or not equal to zero. Preferably, less than 4, more preferably less than 3, and most preferably 1 or 2 of X, X', X", Y' and Y" are nitrogen or nitrogen bonded to oxygen. In addition, it is highly preferred that not more than 1 of X, X', X", Y' and Y" be nitrogen bonded to oxygen; and it is preferred that if one of those species is nitrogen bonded to oxygen, that species is X". Typically, X' is CH, CBr or COR', where R' preferably is benzyl, methyl, ethyl, isopropyl, isobutyl, tertiary butyl or cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl). Most preferably, X" is nitrogen. For certain other preferred compounds X" is C-NR'R", C-OR' or C-NO_2, typically C-NH_2, C-$NHCH_3$ or C-$N(CH_3)_2$, with C-NH_2 being preferred. In certain preferred circumstances, both X' and X" are nitrogen. Typically, X, Y' and Y" each are carbon

bonded to a substituent species, and it is typical that X, Y' and Y" each are carbon bonded to a substituent species such as hydrogen. The individual substituents of X, Y' and Y" (when X, Y' and Y" are carbon bonded to a substituent species) usually include hydrogen, halo (e.g., F, Cl, Br, or I), alkyl (e.g., lower straight chain or branched C_{1-8} alkyl, but preferably methyl or ethyl), or NR'R", where in such case R' and R" are individually hydrogen or lower alkyl, including C_1-C_8, preferably C_1-C_5 alkyl. Typically, X is CH and Y' is CH. However, in certain circumstances, it is preferred that X and Y' both are CH, and Y" is carbon bonded to a non-hydrogen substituent species, such as -NR'R", -OR' or $-NO_2$, such as $-NHCH_3$ or $-N(CH_3)_2$, with $-NH_2$ being most preferred. Adjacent substituents of X, X', Y", X" and Y' (when adjacent X, X', Y", X" and Y' each are carbon bonded to a respective substituent component) can combine to form one or more saturated or unsaturated, substituted or unsubstituted carbocyclic or heterocyclic rings containing, but not limited to, ether, acetal, ketal, amine, ketone, lactone, lactam, carbamate, or urea functionalities. In addition, m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3, preferably is 1or 2, and more preferably is 1.

The substituents of either X, X', X", Y' and Y" (when each respective X, X', X", Y' and Y" is carbon) can include hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, heterocyclyl (e.g., beta-styryl), substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl and substituted arylalkyl functionalities. The substituents of X, X', X", Y' and Y" individually usually include hydrogen, halo (e.g., F, Cl, Br, or I), alkyl (e.g., lower straight chain or branched C_{1-8} alkyl, but preferably methyl or ethyl), or NR'R", where in such case R' and R" are individually hydrogen or lower alkyl, including C_1-C_8, preferably C_1-C_5 alkyl. More specifically, X, X', X", Y' and Y", and most preferably X', can include C-H, C-F, C-Cl, C-Br, C-I, C-R', C-NR'R", $C\text{-}CF_3$, C-OH, C-CN, $C\text{-}NO_2$, $C\text{-}C_2R'$, C-SH, $C\text{-}SCH_3$, $C\text{-}N_3$, $C\text{-}SO_2CH_3$, C-OR', C-SR', C-C(=O)NR'R", C-NR'C(=O)R', C-C(=O)R', C-C(=O)OR', $C(CH_2)_qOR'$, C-OC(=O)R', $C\text{-}(CR'R")_qOCH_2C_2R'$, $C\text{-}(CR'R")_qC(=O)R'$, $C\text{-}O(CR'R")_qC(=O)R'$, $C(CR'R")_qC(CHCH_3)OR'$, $C(CR'R")_qNR'R"$, C-CH=CHR', COC(=O)NR'R" and C-NR'C(=O)OR' where R' and R" are individually hydrogen or lower alkyl (e.g., C_1-C_{10} alkyl, preferably C_1-C_5 alkyl, and more preferably methyl, ethyl, isopropyl or

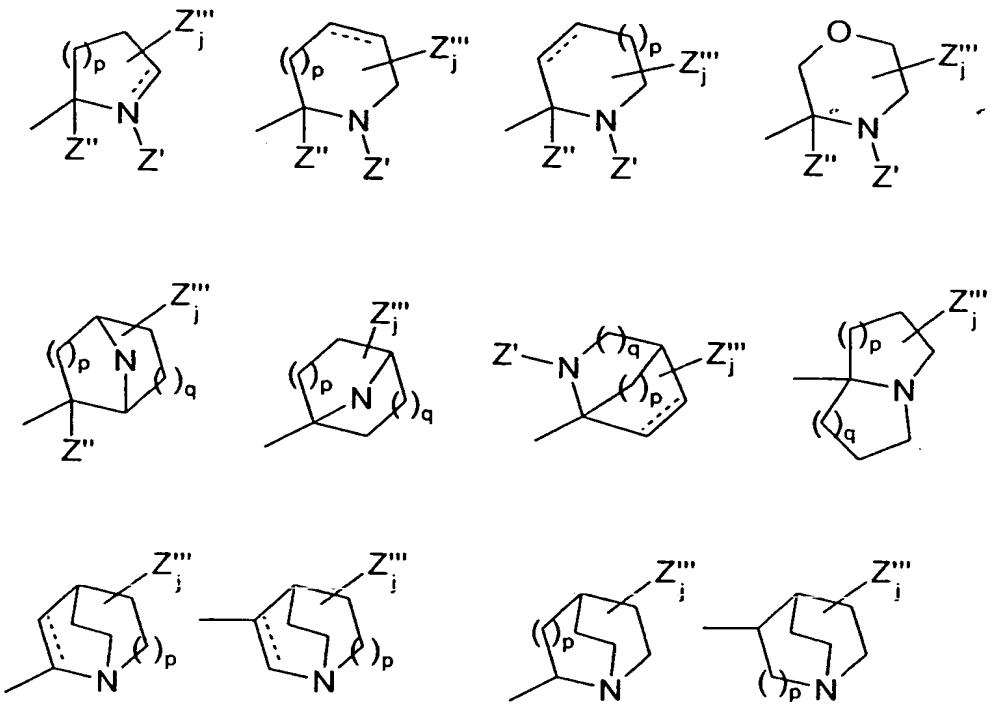
isobutyl), an aromatic group-containing species or a substituted aromatic group-containing species, and q is an integer from 1 to 6. R′ and R″ can be straight chain or branched alkyl, or R′ and R″ can form a cycloalkyl funtionality (e.g., cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and quinuclidinyl). Representative aromatic group-containing species include pyridinyl, quinolinyl, pyrimidinyl, phenyl, and benzyl (where any of the foregoing can be suitably substituted with at least one substituent group, such as alkyl, halo, or amino substituents). Other representative aromatic ring systems are set forth in Gibson et al., *J. Med. Chem.* 39:4065 (1996).

B is a substituted or unsubstituted two carbon bridging species; and typically can be acetylenic or ethylenic, preferably ethylenic. That is, B can be selected from –CC- or –CR'=CR″-, wherein R' and R″ are defined hereinafter, but R' and R″ preferably each are hydrogen. When the two carbon bridging species is ethylenic, that species can have a trans(Z) or cis(E) form, but most preferably is trans(E).

E, E^{I}, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent (e.g., alkyl, substituted alkyl, halo substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl or substituted arylalkyl), preferably lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl) or halo substituted lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as trifluoromethyl or trichloromethyl). Generally all of E, E^{I}, E^{II} and E^{III} are hydrogen, or at least one of E, E^{I}, E^{II} and E^{III} is non-hydrogen and the remaining E, E^{I}, E^{II} and E^{III} are hydrogen. For example, when m is 1 and n is 0, E and E^{I} each can be hydrogen, or E can be hydrogen and E^{I} can be methyl; or when m is 1 and n is 1, E, E^{I}, E^{II} and E^{III} all can be hydrogen, or E, E^{I} and E^{II} can be hydrogen and E^{III} can be methyl, or E^{I}, E^{II} and E^{III} can be hydrogen and E can be methyl. Typically, the selection of m, n, E, E^{I}, E^{II} and E^{III} is such that 0, 1 or 2, usually 0 or 1, and preferably 0, of the substituents designated as E, E^{I}, E^{II} and E^{III} are non-hydrogen (e.g., substituents such as alkyl or halo-substituted alkyl).

Depending upon the selection of E, E^{I}, E^{II} and E^{III}, compounds of the present invention have chiral and geometric centers, and the present invention relates to racemic mixtures of such compounds as well as enamiomeric compounds.

Q is represented as follows:

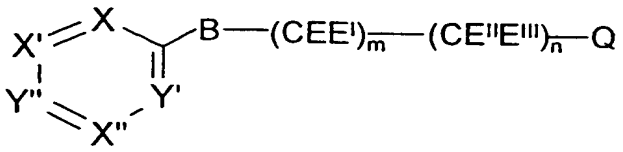


Z′ and Z″ individually represent hydrogen or lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl), substituted alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; and preferably Z′ is hydrogen or methyl, and Z″ is hydrogen. Z‴ is a suitable non-hydrogen substituent, and can include those aforementioned alkyl, acyl, alkoxy, aryloxy, alkoxycarbonyl and aryloxycarbonyl functionalities, as well as -CH=CHR′, -CC-R′, -CH_2SR′ and -CH_2OR′; p is 0, 1 or 2, preferably 0 or 1, and most preferably 1; q is 0, 1, 2 or 3, preferably 0 or 1, and most preferably 1; and j is an integer from 0 to 3, preferably 0 or 1, and most preferably 0. That is, it is possible for the associated carbon and nitrogen atoms can combine to form a monocyclic ring structure such as azetidinyl, pyrrolidinyl, piperidinyl or piperazinyl (optionally substituted with pyridinyl, such as 3-pyridinyl, or pyrimidinyl, such 5-pyridinyl) or a bicyclic ring structure such as 3-(2-azabicyclo[4.2.0]octyl), 3-(2-azabicyclo[2.2.2]octyl), or 3-(2-azabicyclo[2.2.1]heptyl). However, it is preferred that when m is 1 and n is 0, neither E^{II} nor E^{I} are substituted or unsubstituted aryl, heteroaryl, benzhydryl or benzyl. It also is possible for the associated carbon and nitrogen atoms can combine to form a bicyclic ring structure such as 1-(2-azabicyclo[2.2.1]heptyl), 1-(2-

azabicyclo[3.1.0]hexyl, 3-(8-azabicyclo[3.2.1]octyl), 2-(7-azabicyclo[3.1.1]heptyl), 3-(7-azabicyclo[2.2.1]heptyl or 6-(2-azabicyclo[2.2.1]octyl. It also is prefered that when the associated carbon and nitrogen atoms combine to form azetidinyl, pyrrolidinyl, piperidinyl ring structures, the aromatic ring of the formula is substituted by at least least two positions with nitrogen.

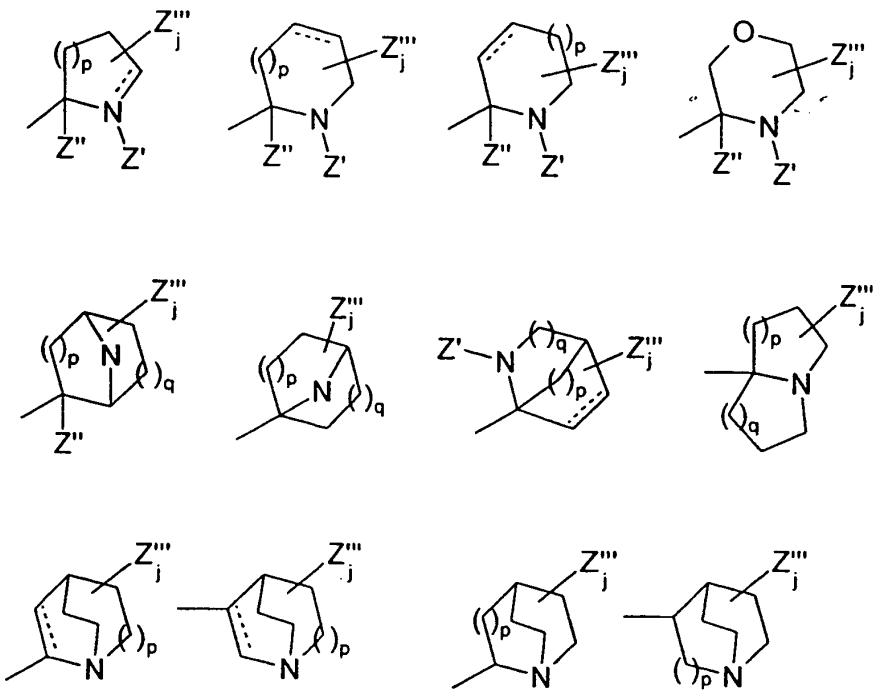
As employed herein, "alkyl" refers to straight chain or branched alkyl radicals including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl; "substituted alkyl" refers to alkyl radicals further bearing one or more substituent groups such as hydroxy, alkoxy, mercapto, aryl, heterocyclo, halo, amino, carboxyl, carbamyl, cyano, and the like; "alkenyl" refers to straight chain or branched hydrocarbon radicals including C_1-C_8, preferably C_1-C_5 and having at least one carbon-carbon double bond; "substituted alkenyl" refers to alkenyl radicals further bearing one or more substituent groups as defined above; "cycloalkyl" refers to saturated or unsaturated cyclic ring-containing radicals containing three to eight carbon atoms, preferably three to six carbon atoms; "substituted cycloalkyl" refers to cycloalkyl radicals further bearing one or more substituent groups as defined above; "aryl" refers to aromatic radicals having six to ten carbon atoms; "substituted aryl" refers to aryl radicals further bearing one or more substituent groups as defined above; "alkylaryl" refers to alkyl-substituted aryl radicals; "substituted alkylaryl" refers to alkylaryl radicals further bearing one or more substituent groups as defined above; "arylalkyl" refers to aryl-substituted alkyl radicals; "substituted arylalkyl" refers to arylalkyl radicals further bearing one or more substituent groups as defined above; "heterocyclyl" refers to saturated or unsaturated cyclic radicals containing one or more heteroatoms (e.g., O, N, S) as part of the ring structure and having two to seven carbon atoms in the ring; "substituted heterocyclyl" refers to heterocyclyl radicals further bearing one or more substituent groups as defined above; "acyl" refers to straight chain or branched alkyl- or substituted alkyl-carbonyl radicals including C_1-C_8, preferably C_1-C_5, such as formyl, acetyl, or propanoyl; "alkoxycarbonyl" refers to an alkyl or substituted alkyl radical attached to an O-carbonyl moiety; and "aryloxycarbonyl" refers to an aryl or substituted aryl radical attached to an O-carbonyl moiety.

Of particular interest are compounds of the formula:



Where Q is described hereinafter; and B, X, X', X", Y', Y", E, E', E", E"', Z', Z", Z"', m, n, j, R' and R" are as defined hereinbefore. The compound prefereably is such that B is an ethylenic bridging species, and as such, the compound can have the cis (Z) or trans (E) form, but most preferably the trans (E) form. Preferably, both R′ and R" are hydrogen, but either or both of R′ and R" can be methyl. Preferably, Z" is hydrogen, and Z' is hydrogen or methyl. Preferably, m is 1, and n is 0 or 1. Preferably, each of E and E' is hydrogen, and preferably E' is hydrogen or methyl, but most preferably both of E and E' are hydrogen. Preferably, each of E" and E"' is hydrogen, and preferably E"' is hydrogen or methyl, but most preferably both of E" and E"' are hydrogen. Preferably, Y" is carbon bonded to a substituent species, and most preferably, that substituent species is hydrogen, halo, NR′R" or OR". Preferably, X" is nitrogen or carbon bonded to a substituent species such as NR′R", NO_2 or OR", but most preferably is nitrogen. Preferably, X' is nitrogen, but also preferably is carbon bonded to a substituent species such as hydrogen, R', halo, OR', NR′R", CC, CN, C_2R' or CHCHR'. Preferably, X and Y' each are carbon bonded to a substituent species, such as hydrogen. Preferably, j is 0 or 1, and preferably Z" is lower alkyl,

such as methyl. Most prreferably, Q is selected from the following:



Representative compounds useful in carrying out the present invention include the following:

(S)-(E)-3-(3-pyrrolidin-2-yl-prop-1-enyl)pyridine

(S)-(E)-3-(2-pyrrolidin-2-ylvinyl)pyridine

3-((2-azetidinylidene)methyl)pyridine

3-((2-methyl-2-azetidinylidene)methyl)pyridine

3-(2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

3-(2-pyrrolidin-2-ylvinyl)pyridine

3-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)pyridine

3-(3-(2-azetidinyl)prop-1-enyl)pyridine

3-(3-(2-methyl-2-azetidinyl)prop-1-enyl)pyridine

3-(3-pyrrolidin-3-ylprop-1-enyl)pyridine

5-((2-azetidinylidene)methyl)pyrimidine

5-((2-methyl-2-azetidinylidene)methyl)pyrimidine

5-(2-(1-methylpyrrolidin-3-yl)vinyl)pyrimidine

5-(2-pyrrolidin-2-ylvinyl)pyrimidine

5-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)pyrimidine

5-(3-(2-azetidinyl)prop-1-enyl)pyrimidine

5-(3-(2-methyl-2-azetidinyl)prop-1-enyl)pyrimidine

5-(3-pyrrolidin-3-ylprop-1-enyl)pyrimidine

3-((2-methyl-2-azetidinylidene)methyl)pyridine

3-(2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

5-((2-methyl-2-azetidinylidene)methyl)pyrimidine

5-(2-(1-methylpyrrolidin-3-yl)vinyl)pyrimidine

3-phenyl-5-(3-pyrrolidin-2-ylprop-1-enyl)pyridine

5-(3-(2-methyl-2-azetidinyl)prop-1-enyl)-3-phenylpyridine

5-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)-3-phenylpyridine

5-(3-(2-methyl-2-azetidinyl)prop-1-enyl)-3-phenylpyridine

3-phenyl-5-(2-pyrrolidin-2-ylvinyl)pyridine

5-(2-(2-azetidinyl)vinyl)-3-phenylpyridine

5-(2-(1-methylpyrrolidin-2-yl)vinyl)-3-phenylpyridine

5-(2-(2-methyl-2-azetidinyl)vinyl)-3-phenylpyridine

3-phenyl-5-(3-pyrrolidin-2-ylprop-1-enyl)pyridine

5-(3-(2-methyl-2-azetidinyl)prop-1-enyl)-3-phenylpyridine

5-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)-3-phenylpyridine

3-phenyl-5-(2-pyrrolidin-2-ylvinyl)pyridine

5-(2-(2-azetidinyl)vinyl)-3-phenylpyridine

5-(2-(1-methylpyrrolidin-2-yl)vinyl)-3-phenylpyridine

5-(2-(1-methylpyrrolidin-2-yl)vinyl)-3-phenylpyridine

1-phenoxy-3-(2-pyrrolidin-3-ylvinyl)benzene

3-(methylethoxy)-5-(2-pyrrolidin-3-ylvinyl)pyridine

3-(methylethoxy)-5-(3-(1-methylpyrrolidin-3-yl)prop-1-enyl)pyridine

3-(methylethoxy)-5-(3-pyrrolidin-3-ylprop-1-enyl)pyridine

3-phenoxy-5-(3-pyrrolidin-3-ylprop-1-enyl)pyridine

5-(2-(2-azetidinyl)vinyl)-3-phenoxypyridine

5-(3-(1-methylpyrrolidin-3-yl)prop-1-enyl)-3-phenoxypyridine

5-(3-(2-azetidinyl)prop-1-enyl)-3-(methylethoxy)pyridine

5-(3-(2-azetidinyl)prop-1-enyl)-3-phenoxypyridine

5-(3-(2-methyl-2-azetidinyl)prop-1-enyl)-3-(methylethoxy)pyridine

5-(3-(2-methyl-2-azetidinyl)prop-1-enyl)-3-phenoxypyridine

1-methoxy-3-(2-(1-methylpyrrolidin-3-yl)vinyl)benzene

1-methoxy-3-(2-(2-methyl-2-azetidinyl)vinyl)benzene

3-ethoxy-5-(2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

3-ethoxy-5-(2-(2-methyl-2-azetidinyl)vinyl)pyridine

3-(methylethoxy)-5-(2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

5-(2-(1-methylpyrrolidin-3-yl)vinyl)-3-phenoxypyridine

5-(2-(2-azetidinyl)vinyl)-3-(methylethoxy)pyridine

5-(2-(2-methyl-2-azetidinyl)vinyl)-3-(methylethoxy)pyridine

5-(2-(2-methyl-2-azetidinyl)vinyl)-3-phenoxypyridine

3-(2-(3-pyridyl)vinyl)-2-aza-2-methylbicyclo[2.2.1]heptane

3-(2-(3-pyridyl)vinyl)-2-azabicyclo[2.2.1]heptane

3-(3-(3-pyridyl)prop-2-enyl)-2-aza-2-methylbicyclo[2.2.1]heptane

3-(3-(3-pyridyl)prop-2-enyl)-2-azabicyclo[2.2.1]heptane

5-(2-(3-pyridyl)vinyl)-1-azabicyclo[3.3.0]octane

5-(3-(3-pyridyl)prop-2-enyl)-1-azabicyclo[3.3.0]octane

7-(2-(3-pyridyl)vinyl)-6-azabicyclo[3.1.1]heptane

7-(4-(3-pyridyl)but-3-enyl)-6-azabicyclo[3.1.1]heptane

1-aza-5-(2-(5-phenyl-3-pyridyl)vinyl)bicyclo[3.3.0]octane

1-aza-5-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[3.3.0]octane

2-aza-2-methyl-3-(2-(5-phenyl-3-pyridyl)vinyl)bicyclo[2.2.1]heptane

2-aza-2-methyl-3-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[2.2.1]heptane

2-aza-3-(2-(5-phenyl-3-pyridyl)vinyl)bicyclo[2.2.1]heptane

2-aza-3-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[2.2.1]heptane

7-aza-2-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[2.2.1]heptane

7-aza-2-(5-phenyl-3-pyridyl)bicyclo[2.2.1]heptane

1-aza-5-(2-(5-phenyl-3-pyridyl)vinyl)bicyclo[3.3.0]octane

1-aza-5-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[3.3.0]octane

2-aza-2-methyl-3-(2-(5-phenyl-3-pyridyl)vinyl)bicyclo[2.2.1]heptane

2-aza-2-methyl-3-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[2.2.1]heptane

2-aza-3-(2-(5-phenyl-3-pyridyl)vinyl)bicyclo[2.2.1]heptane

2-aza-3-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[2.2.1]heptane

7-aza-2-(3-(5-phenyl-3-pyridyl)prop-2-enyl)bicyclo[2.2.1]heptane

7-aza-2-(5-phenyl-3-pyridyl)bicyclo[2.2.1]heptane

6-(2-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)vinyl)-4-aza-1-oxaindene

6-(2-(3-azabicyclo[2.2.1]hept-2-yl)vinyl)-4-aza-1-oxaindene

6-(2-(5-azabicyclo[3.3.0]octyl)vinyl)-4-aza-1-oxaindene

6-(2-(7-azabicyclo[2.2.1]hept-2-yl)vinyl)-4-aza-1-oxaindene

6-(3-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)prop-1-enyl)-4-aza-1-oxaindene

6-(3-(3-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-4-aza-1-oxaindene

6-(3-(5-azabicyclo[3.3.0]octyl)prop-1-enyl)-4-aza-1-oxaindene

6-(3-(7-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-4-aza-1-oxaindene

5-(2-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)vinyl)-3-methoxypyridine

5-(2-(3-azabicyclo[2.2.1]hept-2-yl)vinyl)-3-methoxypyridine

5-(2-(5-azabicyclo[3.3.0]octyl)vinyl)-3-methoxypyridine

5-(2-(7-azabicyclo[2.2.1]hept-2-yl)vinyl)-3-methoxypyridine

5-(3-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-methoxypyridine

5-(3-(3-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-methoxypyridine

5-(3-(5-azabicyclo[3.3.0]octyl)prop-1-enyl)-3-methoxypyridine

5-(3-(7-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-methoxypyridine

5-(2-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)vinyl)-3-(methylethoxy)pyridine

5-(2-(3-azabicyclo[2.2.1]hept-2-yl)vinyl)-3-(methylethoxy)pyridine

5-(2-(5-azabicyclo[3.3.0]octyl)vinyl)-3-(methylethoxy)pyridine

5-(2-(7-azabicyclo[2.2.1]hept-2-yl)vinyl)-3-(methylethoxy)pyridine

5-(3-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-(methylethoxy)pyridine

5-(3-(3-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-(methylethoxy)pyridine

5-(3-(5-azabicyclo[3.3.0]octyl)prop-1-enyl)-3-(methylethoxy)pyridine

5-(3-(7-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-(methylethoxy)pyridine

5-(2-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)vinyl)-3-phenoxypyridine

5-(2-(3-azabicyclo[2.2.1]hept-2-yl)vinyl)-3-phenoxypyridine

5-(2-(5-azabicyclo[3.3.0]octyl)vinyl)-3-phenoxypyridine

5-(2-(7-azabicyclo[2.2.1]hept-2-yl)vinyl)-3-phenoxypyridine

5-(3-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-phenoxypyridine

5-(3-(3-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-phenoxypyridine

5-(3-(5-azabicyclo[3.3.0]octyl)prop-1-enyl)-3-phenoxypyridine

5-(3-(7-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-3-phenoxypyridine

5-(2-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)vinyl)pyrimidine

5-(2-(3-azabicyclo[2.2.1]hept-2-yl)vinyl)pyrimidine

5-(2-(5-azabicyclo[3.3.0]octyl)vinyl)pyrimidine

5-(2-(7-azabicyclo[2.2.1]hept-2-yl)vinyl)pyrimidine

5-(3-(3-aza-3-methylbicyclo[2.2.1]hept-2-yl)prop-1-enyl)pyrimidine

5-(3-(3-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)pyrimidine

5-(3-(5-azabicyclo[3.3.0]octyl)prop-1-enyl)pyrimidine

5-(3-(7-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)pyrimidine

3-((2-azetidinylidene)methyl)pyridine

3-((2-methyl-2-azetidinylidene)methyl)pyridine

3-(2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

3-(2-pyrrolidin-2-ylvinyl)pyridine

3-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)pyridine

3-(3-(2-azetidinyl)prop-1-enyl)pyridine

3-(3-(2-methyl-2-azetidinyl)prop-1-enyl)pyridine

3-(3-pyrrolidin-3-ylprop-1-enyl)pyridine

5-((2-azetidinylidene)methyl)pyrimidine

5-((2-methyl-2-azetidinylidene)methyl)pyrimidine

5-(2-(1-methylpyrrolidin-3-yl)vinyl)pyrimidine

5-(2-pyrrolidin-2-ylvinyl)pyrimidine

5-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)pyrimidine

5-(3-(2-azetidinyl)prop-1-enyl)pyrimidine

5-(3-(2-methyl-2-azetidinyl)prop-1-enyl)pyrimidine

5-(3-pyrrolidin-3-ylprop-1-enyl)pyrimidine

6-(2-(7-azabicyclo[2.2.1]hept-2-yl)vinyl)-4-aza-1-oxaindene

6-(2-pyrrolidin-2-ylvinyl)-4-aza-1-oxaindene

6-(2-(1-methylpyrrolidin-2-yl)vinyl)-4-aza-1-oxaindene

6-(2-(2-azetidinyl)vinyl)-4-aza-1-oxaindene

6-(2-(2-methyl-2-azetidinyl)vinyl)-4-aza-1-oxaindene

6-(2-quinuclidin-2-ylvinyl)-4-aza-1-oxaindene

6-(2-(3-azabicyclo[2.2.1]hept-2-yl)vinyl)-4-aza-1-oxaindene

6-(2-(7-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-4-aza-1-oxaindene

6-(2-pyrrolidin-2-ylvinyl)-4-aza-1-oxaindene

6-(2-(1-methylpyrrolidin-2-yl)prop-1-enyl)-4-aza-1-oxaindene

6-(2-(2-azetidinyl)prop-1-enyl)-4-aza-1-oxaindene

6-(2-(2-methyl-2-azetidinyl)prop-1-enyl)-4-aza-1-oxaindene

6-(2-quinuclidin-2-ylprop-1-enyl)-4-aza-1-oxaindene and

6-(2-(3-azabicyclo[2.2.1]hept-2-yl)prop-1-enyl)-4-aza-1-oxaindene.

The manner, in which certain compounds of the present invention are synthesized can vary. Depending upon the enantiomeric purity of starting materials, compounds of the present invention can be prepared in either racemic form or in enantiomerically pure form. In one method, certain pyridyl olefinic pyrrolidine compounds can be prepared by using a palladium-catalyzed coupling reaction of a 3-bromopyridine or 3-iodopyridine with an olefin possessing a protected pyrrolidine functionally, such as (2S)-2-allyl-1-tert-butoxycarbonylpyrrolidine, also known as (2S)-N-(tert-butoxycarbonyl)-2-(3-prop-1-enyl)pyrrolidine. Reaction conditions employing palladium(II) acetate, tri-o-tolylphosphine, and triethylamine, similar to those described by Frank et. al., *J. Org. Chem.* 43 (15): 2947-2949 (1978) and Malek et. al., *J. Org. Chem.* 47: 5395 (1982) can be used. The tert-butoxycarbonyl protecting group of the resulting reaction product, (2S)-(2E)-N-(tert-butoxycarbonyl)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine can then be removed by treatment with strong acid such as trifluoroacetic acid to produce (2S)-(2E)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine. The pyrrolidine ring can then be N-methylated using aqueous formaldehyde and sodium cyanoborohydride using methodology similar to that described by M. A. Abreo et al., *J. Med. Chem.* 39: 817-825 (1996) to afford (2S)-(2E)-2-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)pyridine. The requisite side chain, (2S)-2-allyl-1-tert-butoxycarbonylpyrrolidine can be prepared from commercially available (Aldrich Chemical Company) (2S)-2-pyrrolidinemethanol. The pyrrolidine nitrogen of the latter compound can be protected by treatment with di-tert-butyl dicarbonate in dichloromethane using triethylamine as a base to produce (2S)-N-(tert-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine. The latter compound can be treated with iodine, triphenylphosphine, and diethyl azodicarboxylate to give (2S)-N-(tert-butoxycarbonyl)-2-(iodomethyl)pyrrolidine. Treatment of the latter compound with vinylmagnesium bromide and copper(I) iodide produces the required olefinic pyrrolidine, (2S)-2-allyl-1-tert-butoxycarbonylpyrrolidine. Because (2R)-2-pyrrolidinemethanol is also commercially available (Aldrich Chemical Company), the corresponding enantiomeric synthetic intermediates and compounds of the present invention can be prepared in a similar fashion, namely (2R)-2-allyl-1-tert-butoxycarbonylpyrrolidine, (2R)-(2E)-N-(tert-butoxycarbonyl)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine, (2R)-(2E)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine and (2R)-(2E)-3-(3-(1-methylpyrrolidine-2-yl)prop-1-enyl)pyridine. Alternatively,

enantiomerically pure 2-pyrrolidinemethanol can be synthetically elaborated to the required chiral olefinic pyrrolidine, 2-allyl-1-tert-butoxycarbonylpyrrolidine using the methodology of M. Ikeda et al., *Heterocycles* 50: 31-34 (1999).

The manner in which certain 5-substituted-pyridyl olefinic pyrrolidine compounds of the present invention are synthesized can vary. In one preferred method, a 5-substituted-3-halo-pyridine compound is subjected to a palladium-catalyzed reaction with an olefinic pyrrolidine compound such as (2S)-2-allyl-1-tert-butoxycarbonylpyrrolidine as described above. Removal of the tert-butoxycarbonyl protecting group affords (2S)-(2E)-2-(3-prop)-1-(5-substituted-3-pyridyl)-1-enyl)pyrrolidine, which can subsequently be N-methylated using aqueous formaldehyde and formic acid. In this manner a number of 5-substituted pyridyl compounds of the present invention can be prepared. In a similar fashion, if one employs a 5-halopyrimidine compound such as 5-bromopyrimidine in this Heck reaction sequence, then the corresponding enantiomerically pure pyrimidine compounds can be prepared, namely (2R)- and (2S)-(2E)-2-(3-prop-1-(5-pyrimidinyl)-1-enyl)pyrrolidine and (2R)- and (2S)-(2E)-5-(3-(1-methylpyrrolidin-2-yl)prop-1-enyl)pyrimidine.

Certain compounds of the present invention possessing a shorter olefinic side chain can be prepared by a variety of methods. In one approach using similar palladium-catalyzed coupling methods, a 3-halopyridine such as a 3-bromopyridine or 3-iodopyridine is coupled with (2S)-2-vinyl-1-tert-butoxycarbonylpyrrolidine. The latter olefinic pyrrolidine compound can be prepared according to the techniques described by M. Ikeda et al., *Heterocycles* 50: 31-34 (1999), starting from commercially available (2S)-2-pyrrolidinemethanol. The protecting group can then be removed from the resulting reaction product, (2S)-(2E)-N-(tert-butoxycarbonyl)-3-(2-pyrrolidin-2ylvinyl)pyridine using trifluoroacetic acid to give (2S)-(2E)-3-(2-pyrrolidin-2-ylvinyl)pyridine. The latter compound can be N-methylated using the previously described methodology. By using (2R)-2-pyrrolidinemethanol, the corresponding enantiomers of the above compounds can be prepared.

In a similar manner, 2-allylquinuclidine can be subjected to a palladium-catalyzed coupling reaction with a 3-halopyridine, such as 3-bromopyridine or 3-iodopyridine to afford 2-(1-(3-pyridyl)propen-3-yl)quinuclidine. The precursor, 2-allylquinuclidine can be prepared from 3-quinuclidinone (commercially available from Aldrich Chemical Company) by alkylation and modified Wolff-Kishner

reduction. Thus, 3-quinuclidinone can be converted to the corresponding imine with isopropylamine and molecular sieves. Alkylation of the imine with lithium diisopropylamine and allyl bromide, followed by hydrolysis produces 2-allyl-3-quinuclidinone. Removal of the carbonyl-protecting group can then be effected by converting the ketone into the p-toluenesulfonyl hydrazone followed by reduction with sodium cyanoborohydride to afford 2-allylquinuclidine.

The manner in which certain pyridyl acetylenic pyrrolidine compounds of the present invention are synthesized can vary. In one method, a palladium-catalyzed reaction can be used for the coupling of a 3-bromopyridine or a 3-iodopyridine with an alkyne possessing a protected pyrrolidine functionality, such as (2S)-N-(tert-butoxycarbonyl)-2-prop-2-ynylpyrrolidine. Reaction conditions employing tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, and a base such as triethylamine and an appropriate solvent, such as 1,2-dimethoxyethane or N,N-dimethylformamide can be used. Alternatively, the methodology set forth in L. Bleicher et al., *Synlett*: 1115 (1995) can be used. The resulting coupling reaction product, (2S)-N-(tert-butoxycarbonyl)-2-(3-(3-pyridyl)prop-2-ynyl)pyrrolidine can then be treated with a strong acid such as trifluoroacetic acid to remove the protecting group producing (2S)-3-(3-pyrrolidin-2-ylprop-1-ynyl)pyridine. The latter compound can be N-methylated by heating with formaldehyde and formic acid to afford (2S)-3-(3-(1-methylpyrrolidin-2-yl)prop-1-ynyl)pyridine. The requisite alkyne, (2S)-N-(tert-butoxycarbonyl)-2-prop-2-ynylpyrrolidine can be prepared by treatment of (2S)-N-(tert-butoxycarbonyl)-2-(iodomethyl)pyrrolidine--the synthesis of which has been previously described above, with the lithium salt of trimethylsilylacetylene or with lithium acetylide, ethylenediamine complex (commercially available from Aldrich Chemical Company) followed by desilylation, if necessary, using potassium fluoride in acetonitrile. The corresponding enantiomers, (2R)-3-(3-pyrrolidin-2-ylprop-1-ynyl)pyridine and (2R)-3-(3-(1-methylpyrrolidin-2-yl)prop-1-ynyl)pyridine can be synthesized from the chiral alkyne, (2R)-N-(tert-butoxycarbonyl)-2-prop-2-ynylpyrrolidine which ultimately can be prepared from (2R)-2-pyrrolidinemethanol (available from Aldrich Chemical Company).

Certain compounds of the present invention possessing a shorter acetylenic side chain can be prepared by a variety of methods. In one synthetic approach, a 3-halopyridine such as 3-bromopyridine can be coupled with an alkyne possessing a protected pyrrolidine functionality such as (2S)-N-(tert-butoxycarbonyl)-2-

ethynylpyrrolidine. Reaction condition employing a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) copper(I) iodide, triethylamine and a solvent such as N,N-dimethylformamide can be used. The resulting reaction product, (2S)-N-(tert-butoxycarbonyl)-3-(2-pyrrolidin-2-ylethynyl)pyridine can be treated with a strong acid such as trifluoroacetic acid to afford (2S)-3-(2-pyrrolidin-2-ylethynyl)pyridine. Treatment of the latter compound with formic acid and formaldehyde or formaldehyde and sodium cyanoborohydride affords the N-methyl analog, (2S)-3-(2-(1-methylpyrrolidin-2-yl)ethynyl)pyridine. The required alkyne (2S)-N-(tert-butoxycarbonyl)-2-ethynylpyrrolidine can be prepared from N-(tert-butoxycarbonyl)-(S)-proline according to the methods described in WO 97/05139 to R. L. Elliot et al. By using the enantiomeric alkyne, (2R)-N-(tert-butoxycarbonyl)-2-ethynylpyrrolidine, prepared from N-(tert-butoxycarbonyl)-(R)-proline, the enantiomers of the above compounds of the present invention can be prepared.

There are a number of methods by which the (Z)-olefinic isomers of pyridyl olefinic pyrrolidine compounds can be synthetically produced. In one approach, these Z-olefinic isomers can be prepared by the controlled hydrogenation of the corresponding alkynylcompunds (e.g., a 3-(3-pyrrolidin-2-ylprop-1-ynyl)pyridine-type compound) using commercially available Lindlar catalyst (Aldrich Chemical Company) using the methodology set forth in H. Lindlar et al., *Org. Syn.* 46: 89 (1966).

The manner in which certain compounds of the present invention are prepared can vary. For example, compounds that possess certain fused-ring heterocycles can be prepared by the Heck reaction. Such compounds can be synthesized by the palladium-catalyzed coupling of a bromo heterocyclic compound, such as 6-bromo-2-methyl-1H-imidazo[4,5-b]pyridine with the previously mentioned olefinic amine side chains, such as (2S)-(2E)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine (also known as (2S)-2-allyl-1-tert-butoxycarbonylpyrrolidine) or (2S)-2-vinyl-1-tert-butoxycarbonylpyrrolidine. Typically, the types of procedures set forth in W. C. Frank et al., *J. Org. Chem.* 43: 2947 (1978) and N. J. Malek et al., *J. Org. Chem.* 47: 5395 (1982) involving a palladium-catalyzed coupling of an olefin and an aromatic halide are used for the coupling reaction. The resulting tert-butoxycarbonyl protected intermediate (Boc-protected) can be deprotonated by treatment with a strong acid, such as trifluroacetic acid. The requisite bromo-imidazopyridine, 6-bromo-2-methyl-1H-imidazo[4,5-b]pyridine can be prepared in 82% yield by heating 2,3-diamino-5-

bromopyridine with acetic acid in polyphosphoric acid according to the methods described by P. K. Dubey et al., *Indian J. Chem.* 16B(6):531-533 (1978). 2,3-Diamino-5-bromopyridine can be prepared in 97% yield by heating 2-amino-5-bromo-3-nitropyridine (commercially available from Aldrich Chemical Company and Lancaster Synthesis, Inc) with tin(II) chloride dihydrate in boiling ethanol according to the techniques described by S. X. Cai et al., *J. Med. Chem.* 40(22): 3679-3686 (1997).

In another example, a bromo fused-ring heterocycle, such as 6-bromo-1,3-dioxolo[4,5-b]pyridine can be coupled with the previously mentioned olefinic amine side chains, using the Heck reaction. The resulting Boc-protected intermediate can be deprotected with a strong acid such as trifluoroacetic acid. The requisite bromo compound, 6-bromo-1,3-dioxolo[4,5-b]pyridine can be synthesized from 5-bromo-2,3-dihydroxypyridine, also known as 5-bromo-3-hydroxy-2(1H)-pyridinone, via a methylenation procedure using bromochloromethane, in the presence of potassium carbonate and N,N-dimethylformamide according to the methodology of F. Dallacker et al., *Z. Naturforsch.* 34 b:1729-1736 (1979). 5-Bromo-2,3-dihydroxypyridine can be prepared from furfural (2-furaldehyde, commercially available from Aldrich Chemical Company and Lancaster Synthesis, Inc) using the methods described in F. Dallacker et al., *Z. Naturforsch.* 34 b:1729-1736 (1979). Alternatively, 5-bromo-2,3-dihydroxypyridine can be prepared according to the techniques described in EP 0081745 to D. Rose and N. Maak.

In an another example of a compound that possesses a fused-ring heterocycle, the bromo compound, 7-bromo-2,3-dihydro-1,4-dioxino[2,3-b]pyridine (also known as 7-bromo-5-aza-4-oxachromane) can be condensed with the previously mentioned olefinic amine side chains. The resulting Boc-protected compound can be deprotected with strong acid such as trifluoroacetic acid. The required bromo compound, 7-bromo-2,3-dihydro-1,4-dioxino[2,3-b]pyridine, can be prepared by treating 5-bromo-2,3-dihydroxypyridine with 1,2-dibromoethane and potassium carbonate in N,N-dimethylformamide according to the methodology of F. Dallacker et al., *Z. Naturforsch.* 34 b:1729-1736 (1979). 5-Bromo-2,3-dihydroxypyridine can be prepared from furfural as described above.

Other polycyclic aromatic compounds of the present invention can be prepared by the Heck reaction. Thus, certain compounds can be synthesized by the palladium-catalyzed coupling of a bromo fused-ring heterocycle, such as 6-bromo-1H-

imidazo[4,5-b]pyridine-2-thiol with the previously mentioned olefinic amine side chains. The Boc-protected intermediate, resulting from the Heck reaction, can be subjected to treatment with a strong acid, such as trifluoroacetic acid. The requisite bromo compound, 6-bromo-1H-imidazo[4,5-b]pyridine-2-thiol can be prepared by treating 6-bromo-1H-imidazo[4,5-b]pyridine with sulfur at 230-260°C according to the methods described in Y. M. Yutilov, *Khim. Geterotsikl Doedin.* 6: 799-804 (1988). 6-Bromo-1H-imidazo[4,5-b]pyridine can be obtained from Sigma-Aldrich Chemical Company. Alternatively, 6-bromo-1H-imidazo[4,5-b]pyridine can be prepared by treating 2,3-diamino-5-bromopyridine with formic acid in polyphosphoric acid using methodology similar to that described by P. K. Dubey et al., *Indian J. Chem.* 16B(6):531-533 (1978). 2,3-Diamino-5-bromopyridine can be prepared in 97% yield by heating 2-amino-5-bromo-3-nitropyridine (commercially available from Aldrich Chemical Company and Lancaster Synthesis, Inc) with tin(II) chloride dihydrate in boiling ethanol according to the techniques described by S. X. Cai et al., *J. Med. Chem.*, 40(22): 3679-3686 (1997). Alternatively, 6-bromo-1H-imidazo[4,5-b]pyridine-2-thiol can be prepared by heating 2,3-diamino-5-bromopyridine with $K^+ {}^-SCSOEt$ in aqueous ethanol using methodology similar to that described by T. C. Kuhler et al., *J. Med Chem.* 38(25): 4906-4916 (1995). 2,3-Diamino-5-bromopyridine can be prepared from 2-amino-5-bromo-3-nitropyridine as described above.

In a related example, 6-bromo-2-phenylmethylthio-1H-imidazo[4,5-b]pyridine can be coupled via Heck reaction with the previously mentioned olefinic amine side chains. The resulting Boc-protected intermediate can be subjected to treatment with a strong acid, such as trifluoroacetic acid. The required bromo compound, 6-bromo-2-phenylmethylthio-1H-imidazo[4,5-b]pyridine can be prepared by alkylating the previously described 6-bromo-1H-imidazo[4,5-b]pyridine-2-thiol with benzyl bromide in the presence of potassium carbonate and N,N-dimethylformamide.

In another example, 6-bromooxazolo[4,5-b]pyridine, can be subjected to palladium catalyzed coupling and deprotection of the resulting intermediate with trifluoroacetic acid. The requisite 6-bromooxazolo[4,5-b]pyridine can be produced from 2-amino-5-bromo-3-pyridinol by condensation with formic acid or a trialkyl orthoformate, using methodology similar to that of M-C. Viaud et al., *Heterocycles* 41: 2799-2809 (1995). The use of other carboxylic acids produces 2-substituted-6-

bromooxazolo[4,5-b]pyridines, which are also substrates for the Heck reaction. The synthesis of 2-amino-5-bromo-3-pyridinol proceeds from furfurylamine (Aldrich Chemical Company). Thus, 5-bromo-3-pyridinol (produced from furfurylamine according to U. S. Patent No. 4,192,946) can be chlorinated, using methods described by V. Koch et al., *Synthesis*, 499 (1990), to give 2-chloro-5-bromo-3-pyridinol, which in turn can be converted to 2-amino-5-bromo-3-pyridinol by treatment with ammonia.

5-Bromooxazolo[5,4-b]pyridine, isomeric by orientation of ring fusion to the previously described 6-bromooxazolo[4,5-b]pyridine, can also be used in the Heck coupling and subsequent deprotection. The required 5-bromooxazolo[5,4-b]pyridine is synthesized from 3-amino-5-bromo-2-pyridinol (3-amino-5-bromo-2-pyridone) by the condensation with formic acid (or a derivative thereof) as described above. 3-Amino-5-bromo-2-pyridinol can be made by bromination (using techniques described by T. Batkowski, *Rocz. Chem.* 41: 729-741 (1967)) and subsequent tin(II) chloride reduction (according to the method described by S. X. Cai et al., *J. Med. Chem.* 40(22): 3679-3686 (1997)) of commercially available 3-nitro-2-pyridinol (Aldrich Chemical Company).

Other polycyclic aromatic compounds of the present invention can be prepared by the Heck reaction. Thus both 5-bromofuro[2,3-b]pyridine and 5-bromo-1H-pyrrolo[2,3-b]pyridine can undergo palladium catalyzed coupling with the previously described olefinic amine side chains. Subsequent removal of the tert-butoxycarbonyl group with trifluoroacetic acid. The requisite 5-bromofuro[2,3-b]pyridine and 5-bromo-1H-pyrrolo[2,3-b]pyridine can be made from 2,3-dihydrofuro[2,3-b]pyridine and 2,3-dihydropyrrolo[2,3-b]pyridine respectively, by bromination (bromine and sodium bicarbonate in methanol) and dehydrogenation (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), using chemistry described by E. C. Taylor et al., *Tetrahedron* 43: 5145-5158 (1987). 2,3-Dihydrofuro[2,3-b]pyridine and 2,3-dihydropyrrolo[2,3-b]pyridine are, in turn, made from 2-chloropyrimidine (Aldrich Chemical Company), as described by A. E. Frissen et al., *Tetrahedron* 45: 803-812 (1989), by nucleophilic displacement of the chloride (with the sodium salt of 3-butyn-1-ol or with 4-amino-1-butyne) and subsequent intramolecular Diels-Alder reaction. Using similar chemistry, 2,3-dihydrofuro[2,3-b]pyridine and 2,3-dihydropyrrolo[2,3-b]pyridine are also produced from 3-methylthio-1,2,4-triazene (E. C. Taylor et al., *Tetrahedron* 43: 5145-5158 (1987)), which in turn is made from glyoxal and S-methylthiosemicarbazide (W. Paudler et al., *J. Heterocyclic Chem.* 7: 767-771 (1970)).

Brominated dihydrofuropyridines, dihydropyrrolopyridines, and dihydropyranopyridines are also substrates for the palladium catalyzed coupling. For instance, both 5-bromo-2,3-dihydrofuro[2,3-b]pyridine and 5-bromo-2,3-dihydropyrrolo[2,3-b]pyridine (from bromination of 2,3-dihydrofuro[2,3-b]pyridine and 2,3-dihydropyrrolo[2,3-b]pyridine, as described above) can be coupled with the previously mentioned olefinic amine side chain in a Heck process and subsequent deprotection. Similarly, 6-bromo-2,3-dihydrofuro[3,2-b]pyridine (isomeric at the ring fusion with the [2,3-b] system) can also be used in a Heck process. The requisite 6-bromo-2,3-dihydrofuro[3,2-b]pyridine can be made from 5-bromo-2-methyl-3-pyridinol by sequential treatment with two equivalents of lithium diisopropylamide (to generate the 2-methylenyl, 3-oxy dianion) and one equivalent of dibromomethane. Alternatively, using chemistry similar to that described by M. U. Koller et al., *Synth. Commun.* 25: 2963-74 (1995), the silyl-protected pyridinol (5-bromo-2-methyl-3-trimethylsilyloxypyridine) can be treated sequentially with one equivalent of lithium diisopropylamide and an alkyl or aryl aldehyde to produce a 2-(2-(1-alkyl- or 1-aryl-1-hydroxy)ethyl)-5-bromo-3-(trimethylsilyloxy)pyridine. Such materials can be converted, by methods (such as acid catalyzed cyclization or the Williamson synthesis) known to those skilled in the art, into the corresponding cyclic ethers (2-alkyl- or 2-aryl-6-bromo-2,3-dihydrofuro[3,2-b]pyridines. Similar chemistry, in which epoxides (instead of aldehydes) are used in reaction with the pyridylmethyl carbanion, leads to 2-alkyl- and 2-aryl-7-bromo-2,3-dihydropyrano[3,2-b]pyridines. These 2-substituted, brominated dihydrofuro- and dihydropyranopyridines are also substrates for the Heck reaction. For instance, 6-bromo-2,3-dihydro-2-phenylfuro[3,2-b]pyridine can be coupled, in a palladium catalyzed process, and the coupling product treated with trifluoroacetic acid.

The 5-bromo-2-methyl-3-pyridinol, required for the syntheses of the brominated dihydrofuro- and dihydropyranopyridines, is produced by standard transformations of commercially available materials. Thus, 2-methylnicotinic acid (Aldrich Chemical Company) can be converted, by sequential treatment with thionyl chloride, bromine, and ammonia (methodology described by C. V. Greco et al., *J. Heterocyclic Chem.* 7: 761-766 (1970)), into 5-bromo-2-methylnicotinamide. Hofmann rearrangement of 5-bromo-2-methylnicotinamide with hypochlorite will give 3-amino-5-bromo-2-methylpyridine, which can be converted to 5-bromo-2-methyl-3-pyridinol by diazotization with sodium nitrite in aqueous sulfuric acid.

Alternatively, alanine ethyl ester (Aldrich Chemical Company) is converted (using ethyl formate) into its N-formyl derivative, which is then converted to 5-ethoxy-4-methyloxazole using phosphorous pentoxide (N. Takeo et al., Japan Patent No. 45,012,732). Diels-Alder reaction of 5-ethoxy-4-methyloxazole with acrylonitrile gives 5-hydroxy-6-methylnicotinonitrile (T. Yoshikawa et al., *Chem. Pharm. Bull.* 13: 873 (1965)), which is converted to 5-amino-2-methyl-3-pyridinol by hydration (nitrile ⇒ amide) and Hofmann rearrangement (Y. Morisawa et al., *Agr. Biol. Chem.* 39: 1275-1281 (1975)). The 5-amino-2-methyl-3-pyridinol can then be converted, by diazotization in the presence of cuprous bromide, to the desired 5-bromo-2-methyl-3-pyridinol.

The manner in which certain aryl substituted olefinic amine compounds possessing an azetidinyl moiety can vary. Using one synthetic approach, 3-(2-(azetidinyl)vinyl)pyridine can be synthesized starting from commercially azetidine-4-carboxylic acid (Aldrich Chemical Company). Azetidine-4-carboxylic acid can be reduced by any of a number of methods common to the art, such as treatment with lithium aluminum hydride to give (2-azetidinyl)methan-1-ol. Protection of the azetidinyl nitrogen of the latter compound can be accomplished by treatment with t-butylpyrocarbonate and base to give N-t-butyloxycarbonyl (N-t-BOC) protected (2-azetidinyl)methan-1-ol, using methodology similar to that described by Carpino et al., *Acc. Chem. Res*, 6:191 (1973). This alcohol can be converted to the alkyl iodide using diethyl azodicarboxylate, triphenylphosphine and iodine according to the procedure of Mitsunobu, see for example: Mitsunobu, *Synthesis* 1:1-28, (1981). Treatment N-t-BOC-4-(iodomethyl)azetidine with magnesium under anhydrous conditions, followed by pyridine-3-carboxaldehyde can afford the Grignard product, N-t-BOC-2-(2-azetidinyl)-1-(3-pyridyl)ethan-1-ol. Treatment of the latter compound with methanesulfonyl chloride gives the O-mesylate which can in turn be eliminated to give N-t-BOC-3-(2-(azetidinyl)vinyl)pyridine using 1,8-diazabicyclo[5.4.0]undec-7-ene in accordance with the method described by Wolkoff, *J. Org. Chem.*, 47:1944 (1982). Finally the t-BOC protecting group can be removed under acidic conditions, such as treatment with trifluoroacetic acid, to give the desired product 3-(2-(azetidinyl)vinyl)pyridine.

The manner in which certain aryl substituted olefinic amine compounds possessing an azabicyclo[2.2.1]heptane functionality can vary. 2-(2-(3-Pyridyl)vinyl-

7-azabicyclo[2.2.1]heptane can be synthesized starting with ethyl 7-aza-7-(ethoxycarbonyl)bicyclo[2.2.1]heptane-2-carboxylate which can be generated from commercially avaliable tropinone (Lancaster Chemical Company) according to the method of Badio et al., *Eur. J. Pharmacol.*, 321:865 (1997). This compound can then be reduced to ethyl 7-aza-2-(hydroxymethyl)bicyclo[2.2.1]heptane-7-carboxylate using excess diisobutylaluminum hydride. This alcohol can then be converted to ethyl 7-aza-2-(iodomethyl)bicyclo[2.2.1]heptane-7-carboxylate using diethyl azodicarboxylate, triphenylphosphine and iodine according to the procedure of Mitsunobu, see for example: Mitsunobu, *Synthesis* 1:1-28, (1981). Conversion of ethyl 7-aza-2-(iodomethyl)bicyclo[2.2.1]heptane-7-carboxylate to the magnesium Grignard reagent, followed by reaction with pyridine 3-carboxaldehyde can afford the alcohol, ethyl 2-(2-(3-pyridyl)-2-hydroxyethyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate. Treatment of the latter compound with methanesulfonyl chloride yields the O-mesylate which can in turn be eliminated to give ethyl 2-(2-(3-pyridyl)vinyl-7-azabicyclo[2.2.1]heptane-7-carboxylate using 1,8-diazabicyclo[5.4.0]undec-7-ene in accordance with the method described by Wolkoff, *J. Org. Chem.*, 47:1944 (1982). The desired product, 2-(2-(3-pyridyl)vinyl-7-azabicyclo[2.2.1]heptane, can be obtained by treatment of the latter compound with refluxing aqueous hydrochloric acid.

The manner in which cetian aryl substituted olefinic amine compounds possessing a 2-azabicyclo[2.2.1]heptane moiety can vary. In one synthetic approach ethyl 3-aza-3-((4-toluenesulfonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate, synthesized according to the method of Hamley et al., *Synlett*, 1:29 (1991), can be reduced to 2-aza-3-(hydroxymethyl)-2-((4-toluenesulfonyl)bicyclo[2.2.1]hept-5-ene using an excess of diisobutyllithium hydride at 0°C. Reduction of the olefin can be accomplished by various methods known to the art, such as hydrogenation over palladium catalyst, to give 2-aza-3-(hydroxymethyl)-2-((4-toluenesulfonyl)bicyclo[2.2.1]heptane This alcohol can then be converted to 2-aza-3-(iodomethyl)-2-((4-toluenesulfonyl)bicyclo[2.2.1]heptane using diethyl azodicarboxylate, triphenylphosphine and iodine according to the procedure of Mitsunobu, see for example: Mitsunobu, *Synthesis* 1:1-28, (1981). Conversion of the latter alkyl iodide to the Grignard reagent followed by reaction with pyridine 3-carboxaldehyde can afford 3-(2-(3-pyridyl)-2-hydroxyethyl)-2-aza-2-((4-

toluenesulfonyl)bicyclo[2.2.1]heptane. Treatment of the latter compound with methanesulfonyl chloride yields the O-mesylate which can in turn be eliminated to give 3-(2-(3-pyridyl)vinyl)-2-aza-2-((4-toluenesulfonyl)bicyclo[2.2.1]heptane using 1,8-diazabicyclo[5.4.0]undec-7-ene in accordance with the method described by Wolkoff, *J. Org. Chem.*, 47:1944 (1982). Finally, the desired product 3-(2-(3-pyridyl)vinyl)-2-azabicyclo[2.2.1]heptane, can be obtained by treatment of the aforementioned N-tosylate with sodium naphthylide according to the procedure of Ji et al., *J. Am. Chem. Soc.* 89:5311 (1967).

The manner in which cetian aryl substituted olefinic amine compounds possessing a 1-azabicyclo[3.3.0]octane moiety can vary. In one synthetic approach, 5-(2-(3-pyridyl)vinyl)-1-azabicyclo[3.3.0]octane can be synthesized by first reacting 1-azabicyclo[3.3.0]oct-1(5)-ene perchlorate (Miyano et al., *Synthesis* 1:701 (1978)) with allylmagnesium bromide to give 1-aza-5-prop-2-enylbicyclo[3.3.0]octane. Then 1-aza-5-prop-2-enylbicyclo[3.3.0]octane and 3-bromopyridine can be coupled using Heck methodology to give the desired product 5-(2-(3-pyridyl)vinyl)-1-azabicyclo[3.3.0]octane. Appropriate examples of Heck procedures (palladium catalyst, phosphine ligand and appropriate base) are set forth in Frank et al., *J. Org. Chem.* 43:2947 (1978) and Malek et al., *J. Org. Chem.* 47:5395 (1982).

The present invention relates to a method for providing prevention of a condition or disorder to a subject susceptible to such a condition or disorder, and for providing treatment to a subject suffering therefrom. For example, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of a CNS disorder (i.e., provide protective effects), amelioration of the symptoms of a CNS disorder, and amelioration of the recurrence of a CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are set forth hereinbefore. Optically active compounds can be employed as racemic mixtures or as enantiomers. The compounds can be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts). Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate.

maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates. Representative salts are provided as described in U.S. Patent Nos. 5,597,919 to Dull et al., 5,616,716 to Dull et al. and 5,663,356 to Ruecroft et al.

The present invention relates to a method for providing prevention of a condition or disorder to a subject susceptible to such a condition or disorder, and for providing treatment to a subject suffering therefrom. For example, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of a CNS disorder (i.e., provide protective effects), amelioration of the symptoms of a CNS disorder, and amelioration of the reoccurrence of a CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are set forth hereinbefore. The present invention also relates to prodrug derivatives of the compounds of the present invention. The compounds normally are not optically active. However, certain compounds can possess substituent groups of a character so that those compounds possess optical activity. Optically active compounds can be employed as racemic mixtures or as enantiomers. The compounds can be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts). Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic

amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates.

Compounds of the present invention are useful for treating those types of conditions and disorders for which other types of nicotinic compounds have been proposed as therapeutics. See, for example, Williams et al. *DN&P* 7(4):205-227 (1994), Arneric et al., *CNS Drug Rev.* 1(1):1-26 (1995), Arneric et al., *Exp. Opin. Invest. Drugs* 5(1):79-100 (1996), Bencherif et al., *JPET* 279:1413 (1996), Lippiello et al., *JPET* 279:1422 (1996), Damaj et al., *Neuroscience* (1997), Holladay et al., *J. Med. Chem* 40(28): 4169-4194 (1997), Bannon et al., *Science* 279: 77-80 (1998), PCT WO 94/08992, PCT WO 96/31475, and U.S. Patent Nos. 5,583,140 to Bencherif et al., 5,597,919 to Dull et al., and 5,604,231 to Smith et al the disclosures of which are incorporated herein by reference in their entirety. Compounds of the present invention can be used as analgesics, to treat ulcerative colitis, to treat a variety of neurodegenerative diseases, and to treat convulsions such as those that are symtematic of epilepsy. CNS disorders which can be treated in accordance with the present invention include presenile dementia (early onset Alzheimer's disease), senile dementia (dementia of the Alzheimer's type), HIV-dementia, multiple cerebral infarcts, Parkinsonism including Parkinson's disease, Pick's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome. Compounds of the present invention also can be used to treat conditions such as syphillis and Creutzfeld-Jakob disease.

The pharmaceutical composition also can include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, anticoagulants, buffering agents, anti-inflammatory agents, anti-pyretics, time release binders, anaesthetics, steroids and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which may be posed as a result of administration of the pharmaceutical composition. In certain circumstances, a compound of the present invention can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular disorder.

The manner in which the compounds are administered can vary. The compounds can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al., the disclosure of which is incorporated herein in its entirety); topically (e.g., in lotion form); orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid carrier); intravenously (e.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids); intrathecally; intracerebro ventricularly; or transdermally (e.g., using a transdermal patch). Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition or formulation for efficient and effective administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compounds can be administered in the form of a tablet, a hard gelatin capsule or as a time release capsule. As another example, the compounds can be delivered transdermally using the types of patch technologies available from Novartis and Alza Corporation. The administration of the pharmaceutical compositions of the present invention can be intermittent, or at a gradual, continuous, constant or controlled rate to a warm-blooded animal, (e.g., a mammal such as a mouse, rat, cat, rabbit, dog, pig, cow, or monkey); but advantageously is preferably administered to a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Administration preferably is such that the active ingredients of the pharmaceutical formulation interact with receptor sites within the body of the subject that effect the functioning of the CNS. More specifically, in treating a CNS disorder administration preferably is such so as to optimize the effect upon those relevant receptor subtypes which have an effect upon the functioning of the CNS, while minimizing the effects upon muscle-type receptor subtypes. Other suitable methods for administering the compounds of the present invention are described in U.S. Patent No. 5,604,231 to Smith et al.

The appropriate dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. By "effective amount", "therapeutic amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the

disorder. Thus, when treating a CNS disorder, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject, and to activatie relevant nicotinic receptor subtypes (e.g., provide neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder). Prevention of the disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount sufficient to activate relevant receptors to effect neurotransmitter (e.g., dopamine) release but the amount should be insufficient to induce effects on skeletal muscles and ganglia to any significant degree. The effective dose of compounds will of course differ from patient to patient but in general includes amounts starting where CNS effects or other desired therapeutic effects occur, but below the amount where muscular effects are observed.

Typically, the effective dose of compounds generally requires administering the compound in an amount of less than 5 mg/kg of patient weight.
Often, the compounds of the present invention are administered in an amount from less than about 1 mg/kg patent weight, and usually less than about 100 ug/kg of patient weight, but frequently between about 10 ug to less than 100 ug/kg of patient weight. For compounds of the present invention that do not induce effects on muscle type nicotinic receptors at low concentrations, the effective dose is less than 5 mg/kg of patient weight; and often such compounds are administered in an amount from 50 ug to less than 5 mg/kg of patient weight. The foregoing effective doses typically represent that amount administered as a single dose, or as one or more doses administered over a 24 hour period.

For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25 ug/ 24 hr./ patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 500, often does not exceed about 400, and frequently

does not exceed about 300 ug/ 24 hr./ patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 ng/ml, and frequently does not exceed 100 ng/ml.

The compounds useful according to the method of the present invention have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds, which are useful in carrying out the present invention are generally greater than about –0.5, often are greater than about 0, and frequently are greater than about 0.5. The log P values of such typical compounds generally are less than about 3, often are less than about 2, and frequently are less than about 1. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane. See, Hansch, et al., *J. Med. Chem.* 11:1 (1968).

The compounds useful according to the method of the present invention have the ability to bind to, and in most circumstances, cause activation of, nicotinic dopaminergic receptors of the brain of the patient. As such, such compounds have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists. The receptor binding constants of typical compounds useful in carrying out the present invention generally exceed about 0.1 nM, often exceed about 1 nM, and frequently exceed about 10 nM. The receptor binding constants of certain compounds are less than about 100 uM, often are less than about 10 uM and frequently are less than about 5 uM; and of preferred compounds generally are less than about 1 uM, often are less than about 100 nM, and frequently are less than about 50 nM. Though not preferred, certain compounds possess receptor binding constants of less than 10 uM, and even less than 100 uM. Receptor binding constants provide a measure of the ability of the compound to bind to half of the relevant receptor sites of certain brain cells of the patient. See, Cheng, et al., *Biochem. Pharmacol.* 22:3099 (1973).

The compounds useful according to the method of the present invention have the ability to demonstrate a nicotinic function by effectively activating neurotransmitter secretion from nerve ending preparations (i.e., synaptosomes). As such, such compounds have the ability to activate relevant neurons to release or secrete acetylcholine, dopamine, and other neurotransmitters. Generally, typical compounds useful in carrying out the present invention provide for the activation of

dopamine secretion in amounts of at least one third, typically at least about 10 times less, frequently at least about 100 times less, and sometimes at least about 1,000 times less, than those required for activation of muscle-type nicotinic receptors. Certain compounds of the present invention can provide secretion of dopamine in an amount which is comparable to that elicited by an equal molar amount of (S)-(-)-nicotine.

The compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are selective to certain relevant nicotinic receptors, but do not cause significant activation of receptors associated with undesirable side effects at concentrations at least greater than those required for activation of dopamine release. By this is meant that a particular dose of compound resulting in prevention and/or treatment of a CNS disorder, is essentially ineffective in eliciting activation of certain muscle-type nicotinic receptors at concentration higher than 5 times, preferably higher than 100 times, and more preferably higher than 1,000 times, than those required for activation of dopamine release. This selectivity of certain compounds of the present invention against those ganglia-type receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of those compounds to activate nicotinic function of adrenal chromaffin tissue at concentrations greater than those required for activation of dopamine release.

Compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of the progression of CNS disorders, amelioration of the symptoms of CNS disorders, an amelioration to some degree of the reoccurrence of CNS disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as demonstrated by increased effects relating to skeletal muscle. As such, administration of certain compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and certain side effects are avoided. That is, an effective dose of a compound of the present invention is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less than 1/5, and often less than 1/10 that amount sufficient to cause certain side effects to any significant degree.

The pharmaceutical compositions of the present invention can be employed to prevent or treat certain other conditions, diseases and disorders. Exemplary of such diseases and disorders include inflammatory bowel disease, acute cholangitis, aphteous stomatitis, arthritis (e.g., rheumatoid arthritis and ostearthritis), neurodegenerative diseases, cachexia secondary to infection (e.g., as occurs in AIDS, AIDS related complex and neoplasia), as well as those indications set forth in PCT WO 98/25619. The pharmaceutical compositions of the present invention can be employed in order to ameliorate may of the symptoms associated with those conditions, diseases and disorders. Thus, pharmaceutical compositions of the present invention can be used in treating genetic diseases and disorders, in treating autoimmune disorders such as lupus, as anti-infectious agents (e.g, for treating bacterial, fungal and viral infections, as well as the effects of other types of toxins such as sepsis), as anti-inflammatory agents (e.g., for treating acute cholangitis, aphteous stomatitis, asthma, and ulcerative colitis), and as inhibitors of cytokines release (e.g., as is desirable in the treatment of cachexia, inflammation, neurodegenerative diseases, viral infection, and neoplasia), The compounds of the present invention can also be used as adjunct therapy in combination with existing therapies in the management of the aforementioned types of diseases and disorders. In such situations, administration preferably is such that the active ingredients of the pharmaceutical formulation act to optimize effects upon abnormal cytokine production, while minimizing effects upon receptor subtypes such as those that are associated with muscle and ganglia. Administration preferably is such that active ingredients interact with regions where cytokine production is affected or occurs. For the treatment of such conditions or disorders, compounds of the present invention are very potent (i.e., affect cytokine production and/or secretion at very low concentrations), and are very efficacious (i.e., significantly inhibit cytokine production and/or secretion to a relatively high degree).

Effective doses are most preferably at very low concentrations, where maximal effects are observed to occur. Concentrations, determined as the amount of compound per volume of relevant tissue, typically provide a measure of the degree to which that eompound affects cytokine production. Typically, the effective dose of such compounds generally requires administering the compound in an amount of much less than 100 ug/kg of patient weight, and even less than 10u/kg of patient

weight. The foregoing effective doses typically represent the amount administered as a single dose, or as one or more doses administered over a 24 hour period.

For human patients, the effective dose of typical compounds generally requires administering the compound in an amount of at least about 1, often at least about 10, and frequently at least about 25 ug / 24 hr. / patient. For human patients, the effective dose of typical compounds requires administering the compound which generally does not exceed about 1, often does not exceed about 0.75, often does not exceed about 0.5, frequently does not exceed about 0.25 mg / 24 hr. / patient. In addition, administration of the effective dose is such that the concentration of the compound within the plasma of the patient normally does not exceed 500 pg/ml, often does not exceed 300 pg/ml, and frequently does not exceed 100 pg/ml. When employed in such a manner, compounds of the present invention are dose dependent, and as such, cause inhibition of cytokine production and/or secretion when employed at low concentrations but do not exhibit those inhibiting effects at higher concentrations. Compounds of the present invention exhibit inhibitory effects upon cytokine production and/or secretion when employed in amounts less than those amounts necessary to elicit activation of relevant nicotinic receptor subtypes to any significant degree.

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereof. In these examples, all parts and percentages are by weight, unless otherwise noted. Reaction yields are reported in mole percentages.

Examples

Example 1

Determination of Binding to Relevant Receptor Sites

Binding of the compounds to relevant receptor sites was determined in accordance with the techniques described in U.S. Patent No. 5,597,919 to Dull et al. Inhibition constants (Ki values), reported in nM, were calculated from the IC_{50} values using the method of Cheng et al., *Biochem. Pharmacol.* 22:3099 (1973). Low binding constants indicate that the compounds of the present invention exhibit good high affinity binding to certain CNS nicotinic receptors.

Example 2

Neurotransmitter Release From Brain Synaptosomes

Neurotransmitter release was measured using techniques similar to those previously published (Bencherif M, *et al.*:. JPET 279: 1413-1421, 1996).

Rat brain synaptosomes were prepared as follows: Female Sprague Dawley rats (100-200 g) were killed by decapitation after anesthesia with 70% $C0_2$. Brains are dissected, and hippocampus, striatum, and thalamus isolated, and homogenized in 0.32 M sucrose containing 5 mM HEPES pH 7.4 using a glass/glass homogenizer. The tissue was then centrifuged for 1000 x g for 10 minutes and the pellet discarded. The supernatant was centrifuged at 12000 x g for 20 minutes. The resultant pellet was re-suspended in perfusion buffer (128 mM NaCl, 1.2 mM KH_2PO_4, 2.4 mM KCl, 3.2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM HEPES, 1 mM Ascorbic acid, 0.01 mM pargyline HCl and 10 mM glucose pH 7.4) and centrifuged for 15 minutes at 25000 x g. The final pellet was resuspended in perfusion buffer and placed in a water bath (37°C) for 10 minutes. Radiolabeled neurotransmitter is added (30 uL ^{3}H DA, 20 L ^{3}H NE, 10 uL ^{3}H glutamate) to achieve a final concentration of 100 nM, vortexed and placed in a water bath for additional 10 minutes. Tissue-loaded filters is placed onto 11-mm diameter Gelman A/E filters on an open-air support. After a 10-minute wash period, fractions are collected to establish the basal release and agonist applied in the perfusion stream. Further fractions were collected after agonist application to re-establish the baseline. The perfusate was collected directly into scintillation vials and released radioactivity was quantified using conventional liquid scintillation techniques. Release of neurotransmitter was determined in the presence of 10 uM of various ligands and was expressed as a percentage of release obtained with a concentration of 10 uM (S)-(-)-nicotine or 300 uM TMA resulting in maximal effects.

Example 3

Determination of Interaction with Muscle Receptors

The determination of the interaction of the compounds with muscle receptors was carried out in accordance with the techniques described in U.S. Patent No. 5,597,919 to Dull et al. The maximal activation for individual compounds (E_{max}) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine.

Reported E_{max} values represent the amount released relative to (S)-(-)-nicotine on a percentage basis. Low E_{max} values at muscle-type receptors indicate that the compounds of the present invention do not induce activation of muscle-type receptors. Such preferable compounds have the capability to activate human CNS receptors without activating muscle-type nicotinic acetylcholine receptors. Thus, there is provided a therapeutic window for utilization in the treatment of CNS disorders. That is, at certain levels the compounds show CNS effects to a significant degree but do not show undesirable muscle effects to any significant degree. The compounds begin to cause muscle effects only when employed in amounts of many times those required to activate dopamine release.

Example 4

Determination of Interaction with Ganglion Receptors

The determination of the interaction of the compounds with ganglionic receptors was carried out in accordance with the techniques described in U.S. Patent No. 5,597,919 to Dull et al. The maximal activation for individual compounds (E_{max}) was determined as a percentage of the maximal activation induced by (S)-(-)-nicotine. Reported E_{max} values represent the amount released relative to (S)-(-)-nicotine on a percentage basis. Low E_{max} values at ganglia-type receptors indicate that the compounds of the present invention do not induce activation of ganglia-type receptors. Such preferable compounds have the capability to activate human CNS receptors without activating ganglia-type nicotinic acetylcholine receptors. Thus, there is provided a therapeutic window for utilization in the treatment of CNS disorders. That is, at certain levels the compounds show CNS effects to a significant degree but do not show certain undesirable side effects to any significant degree. The compounds begin to cause effects at ganglia only when employed in amounts of many times those required to activate dopamine release.

Example 5

Synthesis of (2S)-(2E)-2-(3-Prop-1-(3-pyridyl)-1-enyl)pyrrolidine hemigalactarate or (S)-(E)-3-(3-pyrrolidin-2-yl-prop-1-enyl)pyridine hemigalactarate

(2S)-N-(tert-Butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine

Under a nitrogen atmosphere, a cold (0°C), stirring solution of (2S)-2-pyrrolidinemethanol (3.00 g, 29.66 mmol, Aldrich Chemical Company), triethylamine (4.3 mL, 3.12 g, 30.85 mmol), in dry dichloromethane (50 mL) was treated in portions over 10 min with di-tert-butyl dicarbonate (7.11 g, 32.58 mmol). The solution was stirred and allowed to warm to ambient temperature overnight. Saturated aqueous $NaHCO_3$ solution (25 mL) was added, and the mixture was extracted with $CHCl_3$ (3 x 50 mL). The combined extracts were dried (K_2CO_3), filtered and concentrated under vacuum producing 5.50 g (92.1%) of a thick, colorless syrup.

(2S)-N-(tert-Butoxycarbonyl)-2-(iodomethyl)pyrrolidine

Under a nitrogen atmosphere, a solution of diethyl azodicarboxylate (4.699 g, 26.98 mmol) in dry tetrahydrofuran (THF) (15 mL) was added drop-wise to a cold (0°C), stirring solution of (2S)-N-(tert-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine (5.37 g, 26.68 mmol), iodine (3.42 g, 13.48 mmol) and triphenylphosphine (7.069 g, 26.95 mmol) in dry THF (50 mL). The mixture was stirred and allowed to warm to ambient temperature overnight. The mixture was concentrated on a rotary evaporator, and the residue was stirred with 5% aqueous $Na_2S_2O_3$ (50 mL). After stirring for 30 min, the mixture was extracted with dichloromethane (4 x 25 mL). The combined dichloromethane extracts were dried (Na_2SO_4), filtered and concentrated. The residue was repeatedly crystallized (three to four times) from dry ether and finally from heptane to give 3.20 g (38.6%) of product.

(2S)-N-(tert-Butoxycarbonyl)-2-(3-prop-1-enyl)pyrrolidine

Under a nitrogen atmosphere, a solution of vinylmagnesium bromide, 1.0 M in tetrahydrofuran (2 mL, 2.00 mmol) was slowly added to a suspension of copper(I) iodide (244.9 mg, 1.28 mmol) in dry diethyl ether (10 mL) at -78°C. Upon completion of the addition, the mixture was warmed to -36°C for 5 min and was then cooled to -78°C. A solution of (2S)-N-(tert-butoxycarbonyl)-2-(iodomethyl)pyrrolidine (200.0 mg, 0.64 mmol) in dry diethyl ether (5 mL) was added over a period of 10 min. The reaction mixture was warmed to -36°C and was stirred at -36°C for 6 h. The resulting dark mixture was treated with saturated aqueous NH_4Cl solution (5 mL) and was stirred while warming to ambient temperature. The

reaction mixture was extracted with diethyl ether (4 x 10 mL). The combined ether extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to yield a pale-yellow oil (200 mg). The product was purified by column chromatography on silica gel eluting with hexane-ethyl acetate (1:1). Fractions containing the product were combined and concentrated under vacuum to afford 100 mg (73.6%) of an oil.

(2S)-(2E)-N-(tert-Butoxycarbonyl)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine

A thick-walled glass pressure tube was charged with (2S)-N-(tert-butoxycarbonyl)-2-(3-prop-1-enyl)pyrrolidine (100.0 mg, 0.47 mmol), 3-bromopyridine (112.3 mg, 0.71 mmol), palladium(II) acetate (10.63 mg, 0.047 mmol), tri-o-tolylphosphine (14.42 mg, 0.074 mmol), triethylamine (1 mL, 7.17 mmol) and acetonitrile (10 mL). The tube was sealed, and the reaction mixture was stirred and heated at 110-120°C for 8 h. After cooling, the tube contents were added to a stirring, saturated aqueous $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$ (4 x 20 mL). The combined $CHCl_3$ extracts were dried (K_2CO_3), filtered and concentrated under vacuum to give a thick, dark syrup (500 mg). The product was purified by column chromatography on silica gel eluting with a gradient of ethyl acetate-hexane (20:80→50:50). Fractions containing the product were combined and concentrated under vacuum to give 75.0 mg (54.9%) of an oil.

(2S)-(2E)-2-(3-Prop-1-(3-pyridyl)-1-enyl)pyrrolidine

Under a nitrogen atmosphere, a cold (0°C), stirring solution of (2S)-(2E)-N-(tert-butoxycarbonyl)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine (50.0 mg, 0.17 mmol) in anisole (1 mL) was treated with trifluoroacetic acid (1 mL). After stirring 30 min, the solution was treated with saturated aqueous $NaHCO_3$ solution, saturated with solid NaCl, and extracted with $CHCl_3$ (5 x 10 mL). The combined $CHCl_3$ extracts were dried (K_2CO_3), filtered and concentrated on a rotary evaporator to a thick, dark syrup. The product was purified by column chromatography on silica gel, eluting with a gradient of $CHCl_3$-CH_3OH (→9:1), containing 1% Et_3N. Selected fractions were combined and concentrated under vacuum to give 20.0 mg (61.3%) of a pale, light-yellow oil.

(2S)-(2E)-2-(3-Prop-1-(3-pyridyl)-1-enyl)pyrrolidine Hemigalactarate

Galactaric acid (10.0 mg, 0.048 mmol) was added to a solution of (2S)-(2E)-2-(3-prop-1-(3-pyridyl)-1-enyl)pyrrolidine (18.0 mg, 0.096 mmol) in absolute ethanol (1 mL). The mixture was heated at 60°C and sonicated. Water (2-3 drops) was added, and the process was repeated 3-4 times producing a clear solution. The solution was filtered and concentrated; ethanol (2 mL) was added to the residue and removed by rotary evaporation. The resulting solid was dissolved in a minimum amount of ethanol and dry diethyl ether was added, producing a cloudy solution. After standing 2 days at ambient temperature, the resulting solid was filtered and washed with ether to give 16.6 mg (59.1%) of a pale, light-yellow solid, mp 138-141°C.

The compound exhibits a Ki of 472 nM, neurotransmittor release of 11%, and binding to muscle of 0% and binding to ganglia of 0%.

Example 6

Synthesis of 2(S)-3-(2-Pyrrolidin-2-ylvinyl)pyridine hemigalactarate or (S)-(E)-3(2-pyrrolidin-2-ylvinyl)pyridine hemigalactarate

(2S)-tert-Butyl 2-(hydroxymethyl)pyrrolidinecarboxylate

Under a nitrogen atmosphere, triethylamine (4.3 mL, 30.85 mmol) was added dropwise to an ice-cold stirred solution of S-pyrrolidin-2-ylmethan-1-ol (3.0 g, 29.64 mmol) in anhydrous dichloromethane (50 mL). Di-tert-butyl dicarbonate (7.11 g, 32.61 mmol) was added over a 10 min period, and the reaction mixture was then allowed to warm to room temperature and stirred for 16 h. Saturated aqueous sodium bicarbonate solution (25 mL) was added and the mixture was extracted with chloroform (3 x 50 mL). The combined chloroform extracts were dried (K_2CO_3), filtered and concentrated under vacuum to give 5.5 g (92.4% yield) of product as a colorless syrup.

(2S)-tert-Butyl 2-formylpyrrolidinecarboxylate

Pyridinium chlorochromate (3.26 g, 15.15 mmol) was added to a solution of (2S)-tert-butyl 2-(hydroxymethyl)pyrrolidinecarboxylate (2.77 g, 13.78 mmol) in dichloromethane (50 mL), and the mixture was stirred at room temperature for 12 h. The solvent was removed on a rotary evaporator to give a dark brown gum which was chromatographed on a silica gel column with ethyl acetate : hexane (1:1, v/v) as eluant. Selected fractions containing the product were combined and concentrated on a rotary evaporator to give 1.45 g (52.9% yield) of a colorless oil.

(2S)-tert-Butyl 2-vinylpyrrolidinecarboxylate

The title compound was prepared according to the procedure of Corey et al., J. Amer. Chem. Soc. 104: 4724 (1982). Thus, n-butyllithium (0.708 mL, 2.5 M solution in hexane) was added to a stirred ice-cold solution of methyl triphenylphosphonium bromide (634.69 mg, 1.776 mmol) in anhydrous diethyl ether (10 mL). The mixture was allowed to warm to room temperature, stirred for 3 h, and was then added dropwise via a canulla to a cold (-78°C) solution of (2S)-tert-butyl 2-formylpyrrolidinecarboxylate (350 mg, 1.77 mmol) in anhydrous diethyl ether (10 mL), under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Saturated aqueous ammonium chloride solution (2 mL) was added, the mixture stirred for 10 min and extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate extracts were dried (K_2CO_3), filtered and concentrated on a rotary evaporator to give a viscous brown oil which was chromatographed on a silica gel column with ethyl acetate : hexane (1:9, v/v) as eluant. Selected fractions containing the product were combined and concentrated under vacuum to afford 310 mg (89.5% yield) of a colorless oil.

(2S)-tert-Butyl 2-(2-(3-pyridyl)vinyl)pyrrolidinecarboxylate

In a sealed pressure tube under a nitrogen atmosphere, 3-bromopyridine (264.67 mg, 1.675 mmol), (2S)-tert-butyl 2-vinylpyrrolidinecarboxylate (300 mg, 1.52 mmol), tri-o-tolylphosphine (46.82 mg, 0.153 mmol), palladium(II) acetate

(34.53 mg, 0.15 mmol), triethylamine (2 mL) and acetonitrile (20 mL) were stirred at 90°C for 14 h. The tube was cooled, the contents were slowly poured into a stirred saturated aqueous sodium bicarbonate solution (20 mL) and extracted with chloroform (4 x 20 mL). The combined chloroform extracts were dried (K_2CO_3), filtered and concentrated under vacuum to give 500 mg of a viscous dark oil which was chromatographed on a silica gel column with an ethyl acetate : hexane gradient (1:4 → 1:1, v/v) as eluant. Selected fractions containing the product were combined and concentrated on a rotary evaporator to give 310 mg (84.0% yield) of pale-yellow oil.

(2S)-3-(2-pyrrolidin-2-ylvinyl)pyridine

Under a nitrogen atmosphere, trifluoroacetic acid (1 mL) was added dropwise to a stirred ice-cold solution of (2S)-tert-butyl 2-(2-(3-pyridyl)vinyl)pyrrolidinecarboxylate (280 mg, 1.021 mmol) in anisole (2 mL). The reaction mixture was allowed to warm to room temperature, stirred for 16 h, neutralized with saturated aqueous sodium bicarbonate solution, then saturated with solid sodium chloride and extracted with chloroform (5 x 10 mL). The combined chloroform extracts were dried (K_2CO_3), filtered and concentrated on a rotary evaporator to give a viscous dark oil, which was chromatographed on a silica gel column (70-230 mesh) with chloroform : methanol (9:1, v/v) : 1% triethylamine as eluant. Selected fractions containing the product were combined and concentrated on a rotary evaporator to give 130 mg (73.1% yield) of a colorless oil.

(2S)-3-(2-pyrrolidin-2-ylvinyl)pyridine hemigalactarate

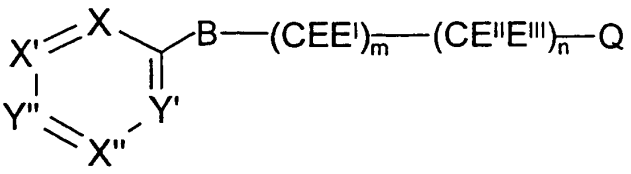
To a stirred solution of (2S)-3-(2-pyrrolidin-2-ylvinyl)pyridine (120 mg, 0.689 mmol) in ethanol (2 mL), galactaric acid (72.41 mg, 0.344 mmol) was added. The mixture was heated at 70°C, sonicated and water (1-2 drops) was added; this process was repeated until most of the solid dissolved. The remaining insoluble material was removed by filtration. To the filtrate anhydrous diethyl ether was added dropwise until it became cloudy. After 16 h at 4°C a precipitate was formed; this was filtered and vacuum dried to give 120 mg (61.9% yield) of product as a light brown solid.

The compound exhibits a Ki of 306 nM and a neurotransmitter release of 48%.

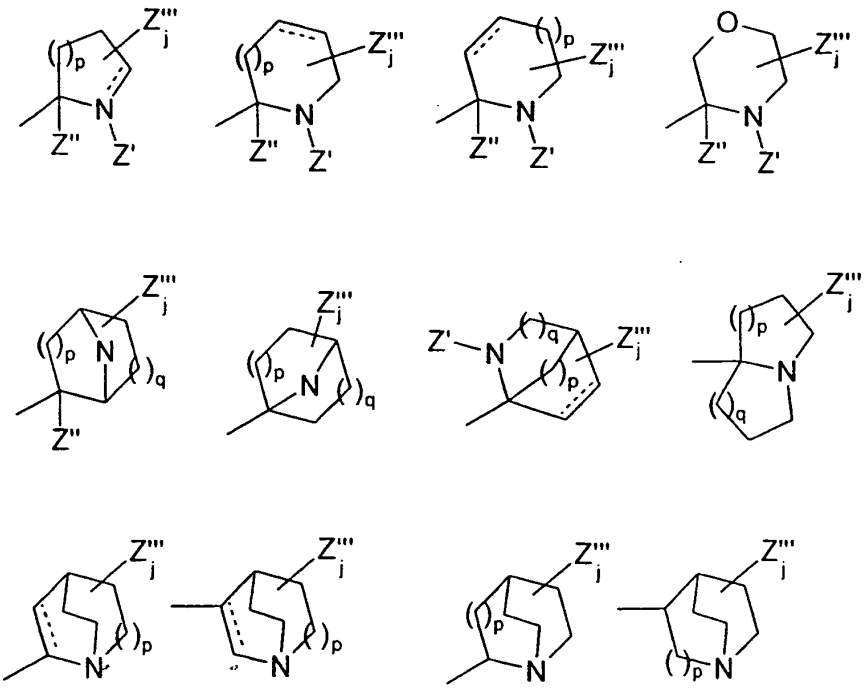
The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED IS:

1. A compound of the formula:



where each of X, X', X", Y' and Y" are individually nitrogen, nitrogen bonded to oxygen or carbon bonded to a substituent species characterized as having a sigma m value between about –0.3 and about 0.75; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; B is a two carbon bridging species; E, E^{I}, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent; and Q is selected from:



where Z′ and Z″ individually represent hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z‴ is a non-hydrogen substituent; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

2. The compound of Claim 1 wherein j is 0.

3. The compound of Claim 1 wherein q is 0 or 1.

4. The compound of Claim 1 wherein Z′ is hydrogen or methyl, and Z″ is hydrogen.

5. The compound of Claim 1 wherein B is acetylenic or ethylenic.

6. The compound of Claim 1 wherein the two carbon bridging species is –CH=CH-, and that species has a trans(Z) form .

7. The compound of Claim 1 wherein the two carbon bridging species is ethylenic, and that species has a trans(Z) form.

8. The compound of Claim 1 wherein all of E, E^{I}, E^{II} and E^{III} individually are hydrogen.

9. The compound of Claim 1 wherein m is 1 and n is 0, and E is hydrogen and E^{I} is methyl.

10. The compound of Claim 1 wherein m is 1 and n is 1, and E, E^{I} and E^{II} each are hydrogen and E^{III} is methyl.

11. The compound of Claim 1 wherein the sum of m plus n is 1or 2.

12. The compound of Claim 1 wherein preferably 1 or 2 of X, X', X″, Y' and Y″ are nitrogen or nitrogen bonded to oxygen.

13. The compound of Claim 1 wherein one of X, X', X", Y' and Y" is nitrogen bonded to oxygen.

14. The compound of Claim 1 wherein the species that is nitrogen bonded to oxygen is X".

15. The compound of Claim 1 wherein X" is nitrogen.

16. The compound of Claim 1 wherein X" is C-NR'R", C-OR' or C-NO_2, where R' and R" are individually hydrogen or lower alkyl.

17. The compound of Claim 1 wherein X" is C-NH_2, C-$NHCH_3$ or C-$N(CH_3)_2$.

18. The compound of Claim 1 wherein both X' and X" are nitrogen.

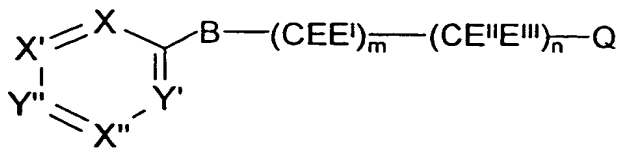
19. The compound of Claim 1 wherein X, Y' and Y" each are carbon bonded to a substituent species.

20. The compound of Claim 1 wherein X and Y' both are CH, and Y" is carbon bonded to a -NR'R", -OR' or -NO_2, where R' and R" are individually hydrogen or lower alkyl.

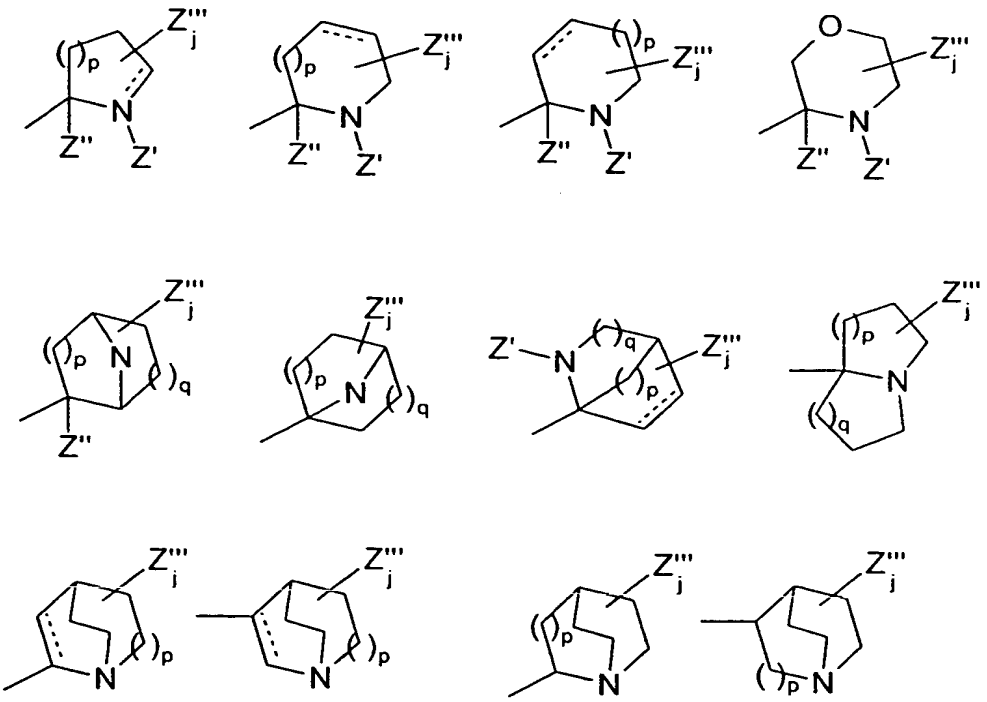
21. The compound of Claim 1, (S)-(E)-3(2-pyrrolidin-2-ylvinyl)pyridine.

22. The compound of Claim 1, (S)-(E)-3-(3-pyrrolidin-2-yl-prop-1-enyl)pyridine.

23. A pharmaceutical composition comprising a compound of the formula:



where each of X, X', X", Y' and Y" are individually nitrogen, nitrogen bonded to oxygen or carbon bonded to a substituent species characterized as having a sigma m value between about –0.3 and about 0.75; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; B is a two carbon bridging species; E, E^{I}, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent; and Q is selected from:



where Z' and Z" individually represent hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z"' is a non-hydrogen substituent; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

24. The pharmaceutical composition of Claim 23 wherein the species that is nitrogen bonded to oxygen is X".

25. The pharmaceutical composition of Claim 23 wherein X" is nitrogen.

26. The pharmaceutical composition of Claim 23 wherein preferably 1 or 2 of X, X', X", Y' and Y" are nitrogen or nitrogen bonded to oxygen.

27. The pharmaceutical composition of Claim 23 wherein one of X, X', X", Y' and Y" is nitrogen bonded to oxygen.

28. The pharmaceutical composition of Claim 23 wherein one of X, X', X", Y' and Y" is nitrogen bonded to oxygen.

29. The pharmaceutical composition of Claim 23 wherein X" is nitrogen.

30. The pharmaceutical composition of Claim 1 wherein X" is C-NR'R", C-OR' or C-NO_2, where R' and R" are individually hydrogen or lower alkyl.

31. The pharmaceutical composition of Claim 23 wherein X" is C-NH_2, C-$NHCH_3$ or C-$N(CH_3)_2$. In certain

32. The pharmaceutical composition of Claim 23 wherein both X' and X" are nitrogen.

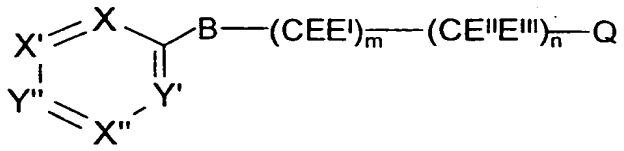
33. The pharmaceutical composition of Claim 23 wherein X, Y' and Y" each are carbon bonded to a substituent species.

34. The pharmaceutical composition of Claim 23 wherein X and Y' both are CH, and Y" is carbon bonded to a -NR'R", -OR' or -NO_2, where R' and R" are individually hydrogen or lower alkyl.

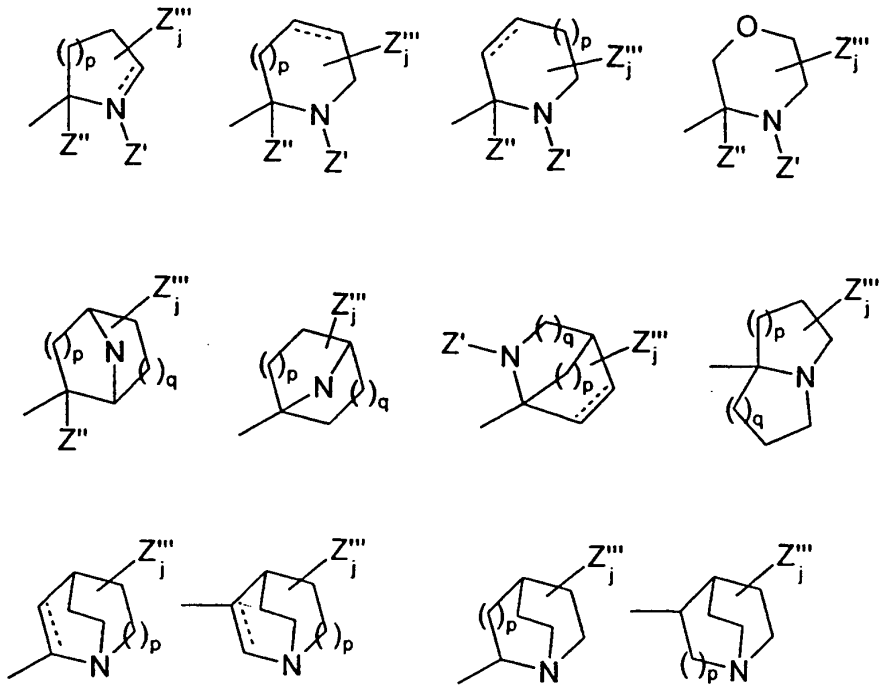
35. The pharmaceutical composition of Claim 23, (S)-(E)-3(2-pyrrolidin-2-ylvinyl)pyridine.

36. The pharmaceutical composition of Claim 23, (S)-(E)-3-(3-pyrrolidin-2-yl-prop-1-enyl)pyridine.

37. A method for treating a central nervous system disorder, said method comprising administering an effective amount of a compound having the formula:



where each of X, X', X", Y' and Y" are individually nitrogen, nitrogen bonded to oxygen or carbon bonded to a substituent species characterized as having a sigma m value between about –0.3 and about 0.75; m is an integer and n is an integer such that the sum of m plus n is 0, 1, 2 or 3; B is a two carbon bridging species; E, E^{I}, E^{II} and E^{III} individually represent hydrogen or a suitable non-hydrogen substituent; and Q is selected from:



where Z′ and Z″ individually represent hydrogen or lower alkyl, acyl, alkoxycarbonyl, or aryloxycarbonyl; Z‴ is a non-hydrogen substituent; the dotted line indicates a carbon-carbon single bond or a carbon-carbon double bond; p is 0, 1 or 2; q is 0, 1, 2 or 3; and j is an integer from 0 to 3.

38. The method of Claim 37 wherein the species that is nitrogen bonded to oxygen is X".

39. The method of Claim 37 wherein X" is nitrogen.

40. The method of Claim 37 wherein preferably 1 or 2 of X, X', X", Y' and Y" are nitrogen or nitrogen bonded to oxygen.

41. The method of Claim 37 wherein one of X, X', X", Y' and Y" is nitrogen bonded to oxygen.

42. The method of Claim 37 wherein one of X, X', X", Y' and Y" is nitrogen bonded to oxygen.

43. The method of Claim 37 wherein X" is nitrogen.

44. The method of Claim 37 wherein X" is C-NR'R", C-OR' or C-NO_2, where R' and R" are individually hydrogen or lower alkyl.

45. The method of Claim 37 wherein X" is C-NH_2, C-$NHCH_3$ or C-$N(CH_3)_2$.

46. The method of Claim 37 wherein both X' and X" are nitrogen.

47. The method of Claim 37 wherein X, Y' and Y" each are carbon bonded to a substituent species.

48. The method of Claim 37 wherein X and Y' both are CH, and Y" is carbon bonded to a -NR'R", -OR' or -NO_2, where R' and R" are individually hydrogen or lower alkyl.

49. The method of Claim 37, (S)-(E)-3(2-pyrrolidin-2-ylvinyl)pyridine.

50. The method of Claim 37, (S)-(E)-3-(3-pyrrolidin-2-yl-prop-1-enyl)pyridine.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 00/18292

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P25/00 A61K31/4406 C07D453/02 C07D213/32 C07D401/06
C07D487/04 C07D209/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 34276 A (DULL GARY MAURICE ;REYNOLDS TOBACCO CO R (US); CROOKS PETER ANTHON) 15 June 2000 (2000-06-15) claims 1,19,25 ---	1,23,37
X	WO 99 32117 A (SIBIA NEUROSCIENCES, INC., USA) 1 July 1999 (1999-07-01) the whole document ---	1,23,37
X	WO 94 14805 A (ZENECA LTD ;WHITTAMORE PAUL ROBERT OWEN (GB)) 7 July 1994 (1994-07-07) claims 1,11; examples --- -/--	1,23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bosma, P

INTERNATIONAL SEARCH REPORT

Int ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SECOR H V ET AL: "THE PREPARATION OF ELONGATED NICOTINE ANALOGUES" HETEROCYCLES,XX,XX, vol. 24, no. 6, 1986, pages 1687-1698, XP000575751 ISSN: 0385-5414 compounds formula 4 ---	1
A	WO 99 00385 A (RAVARD ALAIN ;DEO NIRANJAN MADHUKAR (US); DULL GARY MAURICE (US);) 7 January 1999 (1999-01-07) claims; examples -----	1,23,37

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 00/18292

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		EP 0994875 A	26-04-2000